

201-15345

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HPV Coordinator,

On behalf of BASF, I am submitting the Test Plan and Robust Summaries for Alcohols, C4, distn. Residues (CASNO 68551-11-1). This is an update of a draft submission made on 31 December 2003. The documents have been revised and are now ready for posting and review.

These are in PDF format (unlocked). If you have any questions or require the documents in another format please contact me by phone or email.

Best regards,

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## **Alcohols, C4, distn. residues**

**CAS Number 68551-11-1**

### **A Variable Mixture Also Know as:**

- Butanol Bottoms
- EP-202MP

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## **U.S. EPA HPV Challenge Program Submission**

**December 31, 2003**

**Submitted by:**

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## Executive Overview

EP-202MP (CAS no. 68551-11-1) is the name BASF Corporation uses in the United States for the high-boiling fraction from the hydroformylation of propene. CAS no. 68551-11-1 is a byproduct from the production of butyraldehyde or butanol and is known by several names in commerce including “Butanol Bottoms”, the more specific name EP-202MP, and the TSCA Inventory description “1-Propene, hydroformylation products, high-boiling”. EP-202MP is an amber colored clear liquid with a moderate organic odor and is a variable composition mixture containing about 10 different components at greater than 1% and generally, no single component greater than 20%. It can be used as a chemical solvent but much if it is burned for fuel value. As a result of the limited application of this material and the fact that it is produced in only one plant in the US, the potential for environmental release is limited. Likewise, due to these same factors and its low volatility, the possibility for human exposure is very limited. The chemistry involved in the genesis of EP-202MP is discussed in detail to understand what components are possible, and this information is used to conduct a hazard assessment of the material based on its known and possible components.

2-Ethylhexanol is an important component of the material and was selected, using scientific rationale, as the most representative material with sufficient data that would be an adequate surrogate to represent this variable mixture. Data on EP-202MP itself indicate that it is a biodegradable liquid with low-volatility. Examination of the major components indicate that the mixture is water stable, but components would be rapidly degraded in the atmosphere by indirect photolysis with a half-life less than 15 hours. Water solubility of the individual components ranges from less than 1 mg/L to about 6000 mg/L; overall, the water solubility is low. If released into the environment it is expected to distribute primarily to water and soil.

Hazard to aquatic organisms was estimated from the known aquatic toxicity of the major components. Based on the components it is estimated that this material will have low aquatic toxicity with EC<sub>50</sub> values in the range of 35 to 150 mg/L. Having limited solubility and good biodegradability also reduces environmental concern. Octanol-water partition coefficients were located or estimated for all identified components comprising 1% or more of the mixture. The log K<sub>ow</sub> values range from -0.48 to 5.17 with an average value of 2.4. This attribute combined with biodegradability and rapid metabolism indicate little propensity for bioaccumulation.

EP-202MP demonstrated an acute LD<sub>50</sub> greater than 5000 mg/kg after oral gavage administration to rats of each sex. No repeated administration studies are available for EP-202MP; however, several of its major components have been tested. Data from subchronic oral and inhalation testing of 2-ethylhexanol were selected as appropriate surrogate data to estimate the repeated-dose hazard of EP-202MP. Based on these data, EP-202MP will probably cause peroxisome proliferation at high oral doses in the rat, but administration will be associated with few other effects at daily oral doses of 250 mg/kg or less. By inhalation exposure, no adverse effects are anticipated up to its saturation concentration in air.

Potential genetic effects were assessed via examination of adequate data for most of the major components of EP-202MP. The weight of evidence indicated lack of mutagenic or clastogenic activity for components of EP-202MP. No structural alerts were identified for any of the untested known components. Based on the chemistry and functional group analysis (by carbon-13 NMR), none of the unidentified components are anticipated to have genotoxic activity.

Lack of reproductive toxicity was indicated by the lack of effects on reproductive organs in repeated dose studies of components and surrogates and the lack of developmental toxicity for 2-ethylhexanol. In addition, no reproductive toxicity was observed in a one-generation dietary reproduction study of di-2-ethylhexyl adipate (another surrogate that also encompasses the ester functionality of some EP-202MP components).

Lack of developmental toxicity was also indicated by the one-generation dietary reproduction study of di-2-ethylhexyl adipate where minor fetotoxicity (fetal weights) was observed at maternally toxic doses. In addition, the National Toxicology Program conducted a gavage-administration developmental toxicity study in mice with 2-ethylhexanol; developmental toxicity was not observed at the highest dose tested (194 mg/kg-day).

In summary, although this is a complex and variable mixture, enough is known about its chemistry and overall composition to derive a well-informed hazard characterization based on adequate studies of components and surrogates. There is sufficient confidence in the hazard assessment to consider all the U.S. EPA HPV program data elements as being filled. No additional testing is recommended.

## **Testing Plan and Rationale**

## Testing Plan in Tabular Format

CAS No. 68551-11-1 EP-202MP	Information Available?							
	OECD Study?		GLP Study?		Supporting Information?		Estimation Method?	
HPV Endpoint								
<b>Physical Chemical</b>								
Melting Point	Y	N	N	Y	N	Y	N	
Boiling Point	Y	N	N	Y	N	Y	N	
Vapor Pressure	Y	N	N	N	Y	Y	N	
Partition Coefficient	Y	N	N	N	Y	Y	N	
Water Solubility	Y	N	N	N	Y	Y	N	
<b>Environmental &amp; Fate</b>								
Photo-Degradation	Y	N	N	N	Y	Y	N	
Water Stability	Y	N	N	Y	Y	Y	N	
Transport	Y	N	N	N	Y	Y	N	
Biodegradation	Y	Y	N	Y	N	Y	N	
<b>Ecotoxicity</b>								
Acute Fish	Y	Y	N	Y	N	Y	N	
Acute Invertebrate	Y	Y	N	Y	N	Y	N	
Acute Algae	Y	Y	N	Y	N	Y	N	
<b>Toxicity</b>								
Acute	Y	Y	?	Y	N	Y	N	
Repeated Dose	Y	N	Y	Y	N	Y	N	
Genetic Toxicology "in vitro"	Y	N	Y	Y	N	Y	N	
Genetic Toxicology "in vivo"	Y	N	N	Y	N	Y	N	
Reproductive	N	N	N	Y	N	Y	N	
Developmental	Y	Y	Y	Y	N	Y	N	

## Introduction

The high-boiling fraction from the hydroformylation of propene, CAS no. 68551-11-1, is known by several names in commerce including the more generic name “Butanol Bottoms” and the more specific name EP-202MP used by BASF to designate this particular byproduct. The TSCA Inventory refers to this material as “1-Propene, hydroformylation products, high-boiling” with the following description:

A complex combination of hydrocarbons produced by the distillation of products from the hydroformylation of C3 to C15 alkenes. It consists predominantly of organic compounds such as aldehydes, alcohols, esters, ethers and carboxylic acids having carbon numbers in the range of C4-C16 and boiling in the range of approximately 143°C to 282°C.

Unknown, Variable, Complex, Biological Flag: UVCB

The TSCA Inventory description above is broad, allowing for alkene feedstocks from three carbons to 15 carbons. The High Production Volume (HPV) mixture produced by BASF and described in this document is restricted to the high-boiling fraction derived from the hydroformylation of propene. In spite of this limitation, the TSCA UVCB flag (Unknown, Variable, Complex, Biological Flag) still applies, as this is an indeterminate mixture of chemicals some of which have not been definitively identified.

The objective of the hydroformylation reaction is to prepare aldehydes and alcohols one carbon longer than the feedstock from an alkene and carbon monoxide under reductive conditions using a catalyst. The chemistry is not highly specific and several products are formed by dimerization, partial oxidation and condensation. The crude reaction product is fractionally distilled to remove the desired aldehydes (butyraldehyde and isobutyraldehyde) or alcohols (butanol and isobutanol) that are the major products of the process. What is left behind after distillation is the “high-boiling” fraction and has been assigned the CAS no 68551-11-1 and, in the United States, BASF designates this chemical mixture as EP-202MP, which is the name used in this document. BASF practices this chemistry as a 2-step process with the first step being production of the aldehydes and the second step reduction of the aldehydes to alcohols. Distillation residues from both steps are combined to produce EP-202MP.

EP-202MP is an amber-colored clear liquid with a moderate organic odor (1). Industrial and commercial applications are listed as “chemical solvent”; however, most of the product is utilized for its heat value as a fuel. Estimated production of EP-202MP by BASF in the United States is in the range of 7 to 12 million pounds. United States production of the material is limited to one plant.

Production is in a closed continuous flow reaction system before storage in closed tanks. Shipping is limited to bulk transport by railcar or tank-truck. Occupational exposure in manufacture is restricted by the use of essentially closed systems for production. Inhalation and dermal exposure are possible during sampling and loading/unloading of railcars and tank-trucks but is controlled by the use of personal protective equipment when handling the material outside of the closed manufacturing system. Potential exposure to EP-202MP is also limited by its low volatility; the two major components 2-Ethylhexenal and 2-Ethylhexanal, have estimated vapor pressures of about 3 and 0.6 hPa, respectively. In addition to low volatility, as an unsaturated aliphatic aldehyde,

the more volatile of the two major components is expected to have excellent odoriferous warning properties. If exposure occurs, the duration is expected to be short as this material is produced, stored and transported in closed systems. The potential for exposure is generally limited to sampling, connecting transport equipment and maintenance activities; all of which are short-term exposures.

The composition of EP-202MP is a critical aspect of this HPV analysis; thus, the chemistry of formation of EP-202MP and its typical composition is discussed in detail below in the “chemistry” section of this document.

Several physicochemical, fate and toxicity studies have been conducted with EP-202MP. These studies are briefly reviewed in this testing rationale document, which also describes how these studies meet the SIDS (Screening Information Data Set) end-points of the United States Environmental Protection Agency (USEPA) High Production Volume (HPV) Challenge program. Robust summaries have been prepared for key studies; supporting studies are referenced in these summaries or given as shorter summaries using the IUCLID format. Where specific studies on EP-202MP have not been conducted, data from studies of the major components or other surrogates are provided to fill the HPV endpoint data gaps. In some cases where calculated data are acceptable, a calculation based on the major components has been utilized. The use of acceptable surrogates and acceptable estimation methods are encouraged by the U.S. EPA and other regulatory authorities to avoid unnecessary testing cost and animal usage.

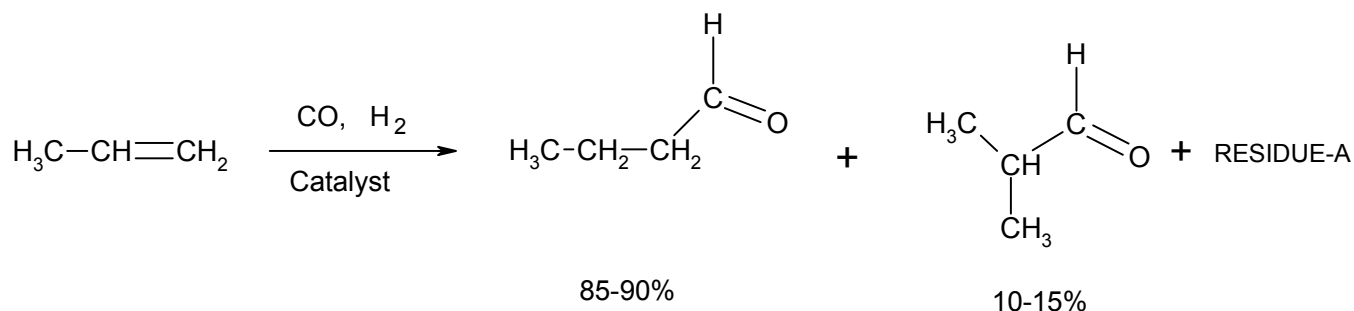
## Chemistry

EP-202MP (CASNO 68551-11-1) is an indeterminate mixture of variable composition derived as a byproduct from a chemical process. To understand how this material relates to other mixtures and pure chemicals that have relevant data and to appreciate the potential range of various components, it is useful to comprehend the process and process variables that contribute to the production of this byproduct mixture.

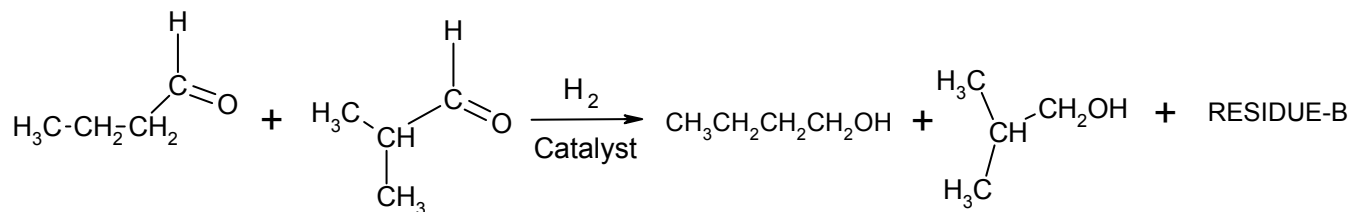
EP-202MP is a residue remaining from the oxo-process synthesis and distillation of butyraldehydes combined with a residue from the subsequent hydrogenation of butyraldehyde and distillation of the resulting butanol. In this particular process, propylene is used as a feedstock and reacted with carbon monoxide and hydrogen over a catalyst to cause carbon monoxide to add to the double bond on either the 1 or the 2 carbon of propylene. Addition to the 1-carbon gives n-butyraldehyde and addition to the 2-carbon gives isobutyraldehyde. Conditions are generally optimized to produce as much of the more valuable n-butyraldehyde as possible. Under the conditions used at BASF, the isobutyraldehyde content ranges from about 10 to 15% of the product. At the temperatures and pressures employed a small amount of the butyraldehyde undergoes condensation reactions (aldol-type) to produce higher molecular weight substances that can undergo reductive or oxidative reactions to give various alcohols and carboxylic acid. During the distillation phase of this continuous process, additional reactions may occur to build higher molecular weight compounds. The process continues in a separate step to produce butanol and isobutanol by catalytic reduction of the distilled aldehydes in different reactor. Similar to the carbonylation reaction, the aldehydes have the opportunity to undergo condensation reactions prior to reduction

producing small quantities of higher molecular weight materials. As the higher molecular weight compounds tend to be less volatile, they remain in the residues from the distillations that comprise EP-202MP.

The primary reaction of this hydroformylation process is:



In the production of EP-202MP, the “heavies” from distillation of the aldehydes are blended with the heavy fraction from the subsequent reduction of butyraldehydes to butanols.

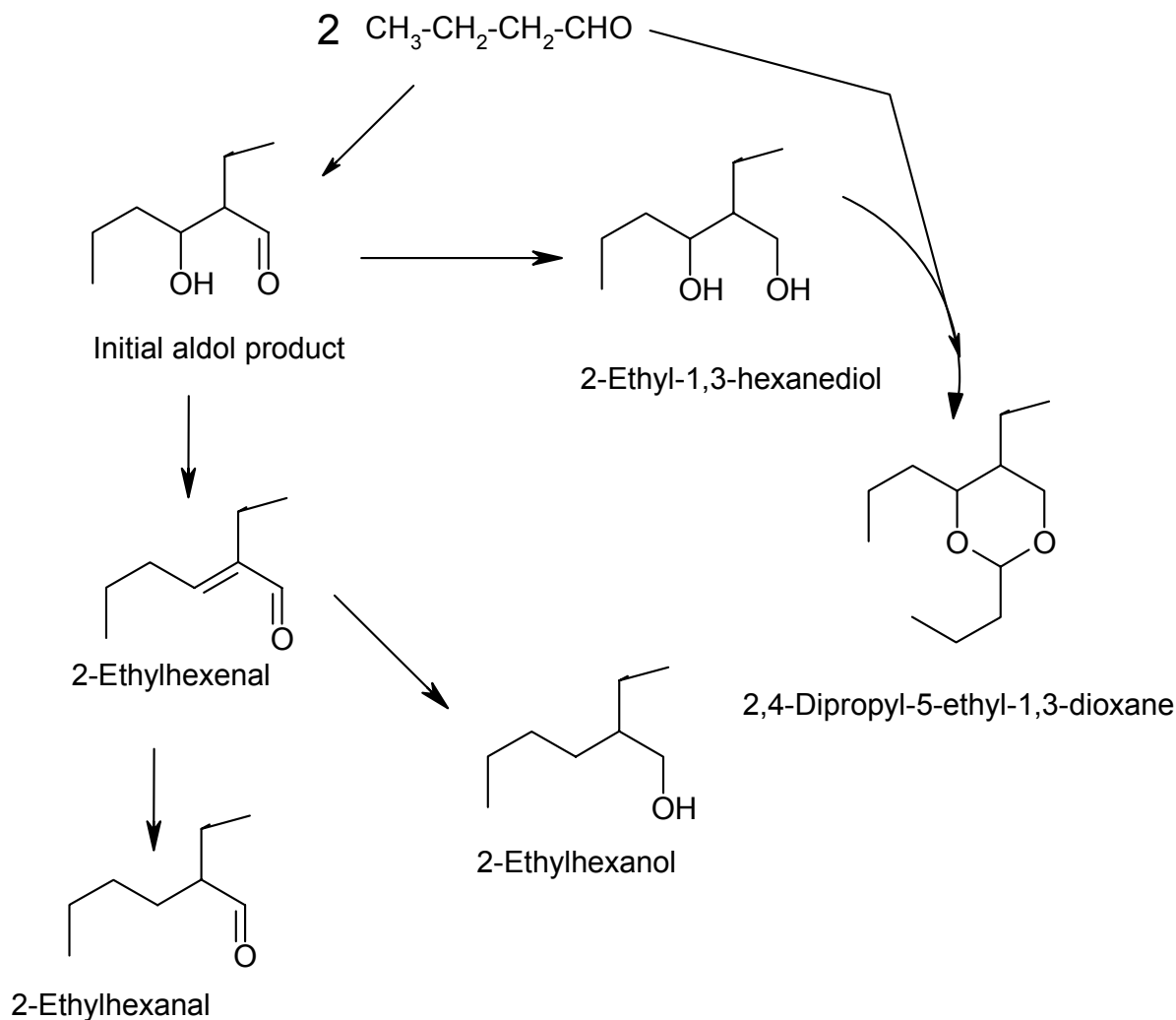


The blend of the “heavies” (Residue-A and Residue-B) is called EP-202MP. The overall process is formally a hydroformylation reaction but it is broken up into two steps to optimize the production of the aldehydes and alcohols.



In either of these reactions, the aldehydes (products in the first instance and starting materials in the second) are considered to be the primary chemically active material leading to the production of “heavies”. Likewise, in each reaction both aldehydes and alcohols are present and the chemistry leading to production of higher molecular weight materials is considered similar.

Aldol type condensation reactions followed by redox reactions can occur to form C8 and larger compounds as shown in Figure 1. In addition to the structures shown, isomers of all three compounds can be formed from the crossed aldol reaction between butyraldehyde and isobutyraldehyde.



**Figure 1. Genesis of EP-202MP C8 + Compounds**

In addition to this series of reactions, simple redox chemistry and ester formation from carboxylic acids and alcohols will occur. The number of potential products is very large, accounting for the complexity of EP-202MP and the reason that many components remain unidentified. Table 1 gives a typical composition for the identified components of EP-202MP.

Chemical Components	CAS No.	Weight % (mean)
2-Ethylhexenal	645-62-5	10.33
2-Ethylhexanal	123-05-7	9.96
n-Butanol	71-36-3	6.77
2-Ethyl-1,3-hexanediol	94-96-2	5.32
2-Ethylhexyl-1,3-dibutyrate		4.12
2,4-Dipropyl-5-ethyl-1,3-dioxane		3.24
n-Butyl-n-butyrate	109-21-7	2.92
N-butyraldehyde	123-72-8	2.47
2-Ethylhexanol	104-76-7	1.57
Isobutanol	78-83-1	0.86
2-Ethylhexyl-butyrate	25415-84-3	0.45
Isobutyraldehyde	78-84-2	0.43
3,5-Diethyl-2-propyltetrahydropyran		0.14
4-Heptanol	589-55-9	0.11
2-Ethylhexyl-butyl ether	62625-25-6	0.08
Butyl butenyl ether		0.07
Isobutyl-n-butyrate	539-90-2	0.03
2-Methylbutanol	137-32-6	0.01
n-Butyl-isobutyrate	97-87-0	0.01
	TOTAL	48.89

**Table 1. Typical Composition of EP-202MP (identified components)**

Additional characterization work using analytical tools such as gas and liquid chromatography combined with mass spectrometry has been conducted to categorize some of the unknowns (Table 2).

EP-202MP Chemical Components	CAS No.	Weight % (range)
C4 Aldehydes		2-8
C4 Alcohols		10-15
C8 Esters		5-10
C8 Aldehydes		10-20
Others, C8 and heavier		50-60
Water		0.1-0.2

**Table 2. Categories of Components in EP-202MP**

In addition to this characterization, a  $^{13}\text{C}$ -NMR spectrum was recorded to gain some assurance that the bulk product was composed of only aliphatic materials or if not, to quantitate any aromatic carbons that might be present. The spectrum is shown as Figure 2 and it can be seen that there is a lack of aromatic carbons, further confirming the homogeneity of the material in spite of it having a large percentage of components that have not been identified. The NMR allows some tentative identifications to be made and some rough estimates of the relative contribution of several types of molecules.

Tentative assignments of some of the carbon signals in a recent batch of EP-202MP is useful in assessing the variety of structures contained in this mixture and are provided in Table 3. It should be noted that the NMR data are primarily confirmatory of the other analysis and consideration of the likely chemical reactions and does not reveal any unanticipated components.

Chemical Shift (ppm)	Tentative Identification	Approx Relative Percent
203- 205	Aldehydes (2 compounds)	2-10% C8 units
170-200	Esters (2 compounds)	2-10 %
145-155	Olefin (1 compound) olefin carbons of $\alpha,\beta$ -unsaturated aldehyde	5-15%
95-105	Acetals or hindered ethers	5-15%
70-80	Alcohols ( $2^\circ$ )	15-40%
60-70	Alcohols ( $1^\circ$ )	20-50%

**Table 3. Tentative Assignments of Carbon Signals in EP-202MP**

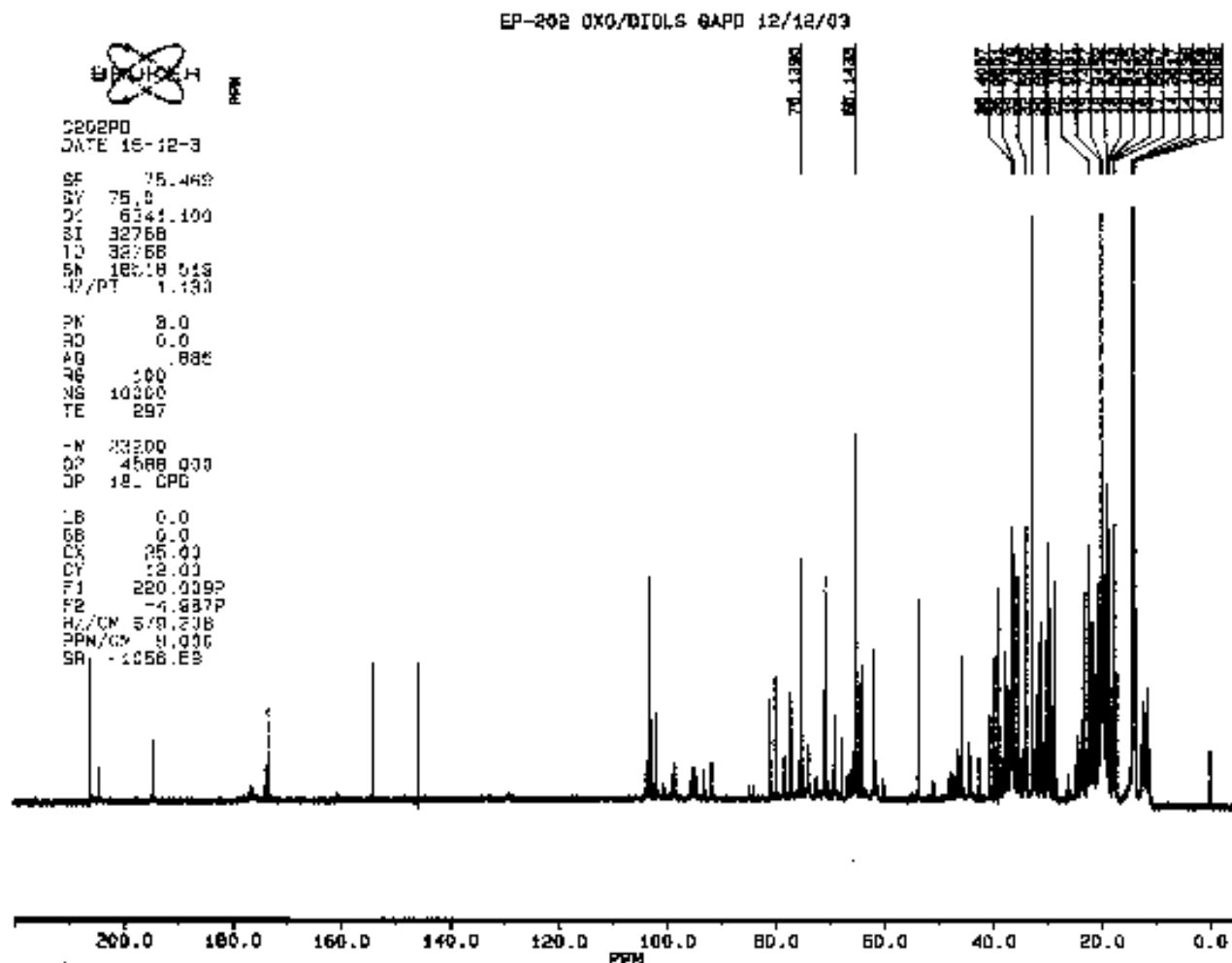


Figure 2.  $^{13}\text{C}$ -NMR spectrum of EP-202MP

## Physicochemical Data

Physicochemical data for EP-202MP are available from manufacturer's information and from EPIWIN estimates and are summarized in Table 4.

Melting Point	ca. $-90^{\circ}\text{C}$ (2)
Boiling Point	$93^{\circ}\text{C}$ (initial) @ 1013 hPa (2)
Vapor Pressure	ca. 1 – 5 hPa @ $25^{\circ}\text{C}$ (3)
Partition Coefficient	$\text{Log } K_{\text{o/w}} = -0.48 - 5.17$ (4)
Water Solubility	Variable, 0.5 – 6000 mg/L (4)

**Table 4: Physicochemical Summary Data for EP-202MP**

The freezing (melting) point and boiling point (initial) are measured properties for typical material as stated on the Technical Data Sheet for EP-202MP. Notice that only the approximate initial boiling point is given, as this is a material that undergoes fractional distillation as it boils.

A single octanol-water partition coefficient cannot be defined as this mixture has a variety of components that have varying hydrophobicities. To understand the potential distribution and bioaccumulative properties of EP-202MP, individual components must be considered. Table 5 contains the EPIWIN estimated log  $K_{\text{o/w}}$  for the nine most prevalent components with concentrations estimated to be greater than 1% of the mixture. In addition to being the materials that actually make up most of EP-202MP, they represent a good cross section of the chemical classes that comprise EP-202MP and are considered representative of the entire sample (5). The  $K_{\text{o/w}}$  spans from  $-0.48$  for butyraldehyde to  $5.17$  for 2-ethylhexyl-1,3-dibutyrate. Although two of the materials have  $K_{\text{o/w}}$  values greater than 3, that indicate bioaccumulation is possible, the one with the highest  $K_{\text{o/w}}$  is an ester, which is expected to be both biodegradable and easily converted by esterases in man and animals to 2-ethyl-1,3-hexanediol and butyric acid that have lower  $K_{\text{o/w}}$  values. The only structures that are of concern from a persistence and potentially bioaccumulative perspective are the simple ethers (e.g. ethylhexyl-butyl ether at less than 0.1% of the material) and the cyclic substituted 1,3-dioxanes (about 3% of the mixture).

Component	SMILES	log Kow*	H <sub>2</sub> O Sol* (mg/L)
2-Ethylhexenal	<chem>CCCC=C(CC)C=O</chem>	2.62 c	586 e
2-Ethylhexanal	<chem>CCCCC(CC)C=O</chem>	2.71 c	108 c
n-Butanol	<chem>CCCCO</chem>	0.88 e	6320 e
2-Ethyl-1,3-hexanediol	<chem>CCCC(O)C(CC)CO</chem>	1.60 c	4200 e
2-Ethylhexyl-1,3-dibutyrate	<chem>CCCC(OC(=O)CCC)C(CC)COC(=O)CCC</chem>	5.17 c	0.56 c
n-Butyl-n-butyrate	<chem>CCCC(=O)OCCCC</chem>	2.83 c	309 c
n-Butyraldehyde	<chem>CCCC=O</chem>	-0.48 e	238 e
2,4-Dipropyl-5-ethyl-1,3-dioxane	<chem>C(CCC)1C(CC)COC(CCC)O1</chem>	3.89 c	20.7 c
2-Ethylhexanol	<chem>CCCCC(CC)CO</chem>	2.73 c	880 e
* e = experimental value from SRC database, c = calculated value using EPIWIN			

**Table 5: Experimental and Calculated Octanol-Water Partitions Coefficients for EP-202MP**

Vapor pressure for EP-202MP is also a variable parameter. It depends initially on the vapor pressure and physicochemical interactions (with other components) of the most volatile components and, as the mixture evaporates and loses the more volatile components, the vapor pressure will decrease. For the purpose of this table for bulk material, the vapor pressure was estimated from the initial boiling point using chemical principles (see robust summary). In the environment after dispersal, individual vapor pressures are a determinant of distribution and individual vapor pressures were taken into consideration in the fugacity calculations.

Water solubility is dependent on the solubility of individual components and on the bulk properties of the material as a whole; in the presence of an organic liquid phase the partition coefficient is as important as the solubility. In addition, with any partially water-soluble mixture, cosolvent effects are expected to play an important role. As this is a variable mixture and cosolvent effects are difficult to model, the experimental or calculated water solubilities are used as reference values, with the understanding that under various conditions the effective solubility could be different. Considering that the composition is mostly higher molecular weight components, the mixture overall is expected to display relatively low water solubility and will form two phases when mixed with water.

**Recommendation:** No additional physicochemical studies are recommended. The available data fill the HPV required data elements with sufficient precision to define the hazards of this variable composition material.

## Environmental Fate and Pathways

### Biodegradation

Biodegradation potential of the “heavy fraction” from the butanol distillation has been determined using oxygen uptake measured with a respirometer (OECD guideline 301C) (6). This material was found to be greater than 60%

biodegradable. Although it is not clear if this result meets the OECD “readily biodegradable” criteria, it is apparent that biodegradability is good on this sample of material. This information is consistent with the structures of the most prevalent compounds; however, it should be taken into consideration that some of the components with linear and cyclic ether structures are probably better characterized as “inherently biodegradable”. Based on inspection of the chemical structures, no component is anticipated to be resistant to biodegradation.

2-Ethylhexanol is considered a reasonable surrogate for the product due to its branched structure and oxidation state. It is known to be biodegradable giving either 55% or 68% biodegradation in 17 days in a Directive 84/449/EEC, C.5 "Biotic degradation – modified Sturm test" (7) and 88% in 17 days in an EEC Directive 79–831 Annex V Part C (1984): Methods for the determination of ecotoxicity. Degradation – Biotic Degradation, Manometric Respirometry test (8). In an inherent biodegradation test (OECD-302B guideline), 2-ethylhexanol was found to degrade more than 95% in only 5 days (9).

Although there are some unresolved issues over the test material meeting the OECD readily biodegradable criteria and the exact extent of 2-ethylhexanol’s biodegradation, overall, there is high confidence that EP-202MP is biodegradable in the environment. It must also be kept in mind that actual testing would involve testing of a variable mixture in a inconsistent test system (source and activity of inoculum will differ); therefore, the existing information indicating relatively facile biodegradation of major components combined with the expectation that ethers and more highly branched structures will biodegrade more slowly is sufficient to meet the requirements of the HPV screening test program.

### **Water Stability**

Water stability has been estimated for the major components of EP-202MP. Most of the components do not contain a water-reactive or hydrolysable group. The aliphatic alcohols and aliphatic ethers that make up the bulk of EP-202MP are considered water stable for this reason (10). The materials that are potentially hydrolysable are the two aliphatic esters. The esters’ structures were entered into the HYDROWIN (v1.67) program to estimate hydrolysis rates (see robust summary for details). This program gave estimates for the second order hydrolysis rate with hydroxyl ion. These rate constants were used to estimate the half-life of these two esters in water at pH 7 and pH 8. The results are shown in Table 6.

Water Stability of EP 202	K <sub>b</sub> (estimated)	Half-life (years)	
Component	(L/mol-sec)	pH 7.0	pH 8.0
2-Ethylhexenal	0	>> 1	> 1
2-Ethylhexanal	0	>> 1	> 1
n-Butanol	0	>> 1	> 1
2-Ethyl-1,3-hexanediol	0	>> 1	> 1
2-Ethylhexyl-1,3-dibutyrate	0.0015	6.2	0.62
n-Butyl-n-butyrate	0.053	4.1	0.41
n-Butyraldehyde	0	>> 1	> 1
2,4-Dipropyl-5-ethyl-1,3-dioxane	0	>> 1	> 1
2-Ethylhexanol	0	>> 1	> 1

**Table 6. Water Stability of EP-202MP Components**

It should be noted that although the aldehydes are estimated to be essentially indefinitely stable in pure water solution (they typically exist in a hydrated form) they will react with organic material found in lakes and waterways and will thus exhibit a shorter abiotic degradation half-life than predicted on only the basis of hydrolysis. In addition, it is estimated that all of the components will biodegrade in natural waters far faster than they will undergo abiotic hydrolysis.

### Photodegradation

Photodegradation was estimated using version 1.90 of the Atmospheric Oxidation Program for Microsoft Windows (AOPWIN) that estimates the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. The estimated rate constant is used to calculate atmospheric half-lives for organic compounds based upon average atmospheric concentrations of hydroxyl radical. The approach used was to take the nine most prevalent (greater than 1%) materials in the preparation and individually determine their reactivity with hydroxyl radical assuming each component will be unaffected by the others after vaporization into the troposphere. The program produced estimated rate constants ranging from  $6.2 \times 10^{-12}$  to  $50.7 \times 10^{-12}$  cm<sup>3</sup>/molecule-sec. Using the default atmospheric hydroxyl radical concentration in APOWIN and the range of estimated rate constants of major components of EP-202MP for reaction with hydroxyl radical, the estimated half-life of EP-202MP vapor in air is approximately 2 to 8 hours. The full details of the calculations are given in the robust summaries and the table below provides a summary of the results.

Regarding the components at less than one percent and the unidentified components, as they have similar empirical formulas (based on the NMR and potential chemical reactions), the reaction rate constants for hydroxyl

radical are going to be similar (see robust summary for example calculations showing the influence of structure on reactivity with hydroxyl radical) indicating rapid photodegradation.

EP-202MP Component	Results of AOP v 1.09 Hydroxyl Radical Reaction Prediction		AOP Ozone Prediction	
	Rate Constant ( $\times 10^{12}$ cm/molec-sec)		Half-life (hrs)	Half-life (hrs)
	Calculated	Experimental		
2-Ethylhexenal	49.99	n	2.6	23.2
2-Ethylhexanal	33.98	n	3.8	nr
n-Butanol	6.89	8.75	14.1*	nr
2-Ethyl-1,3-hexanediol	22.23	n	5.8	nr
2-Ethylhexyl-1,3-dibutyrate	17.53	n	7.3	nr
n-Butyl-n-butyrate	6.24	10.6	12.1*	nr
n-Butyraldehyde	25.43	23.5	5.47*	nr
2,4-Dipropyl-5-ethyl-1,3-dioxane	50.69	n	2.5	nr
2-Ethylhexanol	13.23	n	9.7	nr
	n = not found, nr = no reaction			

**Table 7. Summary of Photodegradation Estimates**

As the calculations show, the primary reaction for this series of material is hydrogen abstraction and the rate increases linearly as the number of abstractable hydrogens increase (see robust summaries for examples). The ether moiety activates adjacent hydrogen atoms toward radical abstraction while the ester is a deactivating influence. Based on the structures, reaction with ozone will not be important. None of the materials will absorb light above 290 nm; thus, direct photolysis in the troposphere will not be significant. In summary, all components are expected to have relatively short atmospheric half-lives reacting primarily with atmospheric hydroxyl radical.

Theoretical Distribution (Fugacity) of EP-202MP in the environment was estimated using the MacKay EQC level III model with standard defaults found in EPIWIN v 3.05 using equal releases to water, soil and air (EPIWIN default) as the means of entry into the environment. The approach used was to take the nine materials represented in the preparation at greater than 1% and individually determine their fugacity assuming that one component will not greatly affect the distribution of the other.

As the measured vapor pressure of EP-202MP is a function of the partial pressures of each component, it is more appropriate to use the individual EPIWIN predicted vapor pressure (or the individual measured vapor pressure) for each component in these calculations. Likewise, individual predicted values for log  $K_{o/w}$ ,  $K_{o/c}$ , and half-lives were utilized. The biodegradation half-lives that were used were EPIWIN generated but were individually evaluated for consistency with the known biodegradability of the preparation and found to be representative.

The entire data set with the values utilized for all parameters is shown in the Robust Summary for distribution in the environment and a summary table is shown below. The components evaluated are representative of the full

spectrum of components contained in EP-202MP and include alcohols, aldehydes, an  $\alpha,\beta$ -unsaturated aldehyde, esters and a substituted dioxane. What is apparent is that the components distribute primarily to water and soil with little in the air or sediment except for the two esters, with n-butyl butyrate being more volatile and 2-ethylhexyl-1,3-dibutyrate distributing in sediment to a significant extent.

EP-202MP Component	%	SMILES	Distribution (Percent)			
			Air	Water	Soil	Sediment
2-Ethylhexenal	10.33	<chem>CCCC=C(CC)C=O</chem>	1.39	34.7	63.7	0.216
2-Ethylhexanal	9.96	<chem>CCCCC(CC)C=O</chem>	2.58	34.1	63.0	0.241
n-Butanol	6.77	<chem>CCCCO</chem>	5.91	49.5	44.5	0.0782
2-Ethyl-1,3-hexanediol	5.32	<chem>CCCC(O)C(CC)CO</chem>	0.34	38.6	61.0	0.0859
2-Ethylhexyl-1,3-dibutyrate	4.12	<chem>CCCC(OC(=O)CCC)C(CC)COC(=O)CCC</chem>	1.59	27.7	48.5	22.2
2,4-Dipropyl-5-ethyl-1,3-dioxane	3.24	<chem>C(CCC)1C(CC)COC(CCC)O1</chem>	0.604	19.7	77.6	2.13
n-Butyl-n-butyrate	2.92	<chem>CCCC(=O)OCCCC</chem>	7.8	35.2	56.8	0.208
n-Butyraldehyde	2.47	<chem>CCCC=O</chem>	3.68	53.5	42.7	0.095
2-Ethylhexanol	1.57	<chem>CCCCC(CC)CO</chem>	4.24	41.2	54.3	0.216

**Table 8: Theoretical Distribution (Fugacity) of EP-202MP in the environment**

**Recommendation:** No additional fate and pathway studies are recommended. The available data fill the HPV required data elements.

## Ecotoxicity

No studies have been conducted on the aquatic toxicity of EP-202MP as a mixture; however, a considerable number of studies have been conducted on many of the major components and others can be reliably estimated using ECOSAR and the appropriate model. These are shown in Table 9.

Aquatic Toxicity of EP-202MP Components (all values in mg/L)						
	2-Ethylhexenal	2-Ethylhexanal	n-Butanol	Diol <sup>^</sup>	Butyraldehyde	2-Ethylhexanol
Approx. percent of EP-202MP	10+%	10%	7%	6%	3%	2%
Fish, 96-hr LC <sub>50</sub>	6.0 (11)	8 (12)	> 1000 (13)	257*	25.8 (14)	17-30 (15)
Daphnia, 48 hour EC <sub>50</sub>	20 (16)	11.5 (17)	> 1000 (13)	268*	195 <sup>#</sup> (14)	39 (15)
Algae, 72 or 96 hour EC <sub>50</sub>	19.3 (18)	52 (17)	> 100 (13)	164*	83 (14)	10-20 (15)
* Estimated using ECOSAR (19) # 24-Hour value			<sup>^</sup> diol = 2-Ethyl-1,3-hexanediol			

**Table 9: Aquatic Toxicity of EP-202MP Components.**

Determination and estimation of the actual ecotoxicity values and the actual solubility of EP-202MP are complicated by the fact that it is a variable mixture and actual environmental conditions are not known. The two major components are aldehydes that are anticipated to have “excess” toxicity to aquatic species over materials such as alcohols that are considered “neutral organics” in modeling (20). Based on this reasoning and the low solubility of neutral organics with higher  $K_{ow}$  values (including the esters in EP-202MP), the aquatic toxicity of EP-202MP will primarily be a function of the aldehyde components and primarily the two in highest concentration, specifically 2-ethylhexenal and 2-ethylhexanal. If these represent about 20 % of the mixture, a rough estimate of the toxicity in a system where all the aldehydes distribute into the water column in an available form would be based on 20 % of the acute value for the species, or:

- ❑ Fish                      ~35 mg/L
- ❑ Daphnids                ~80 mg/L
- ❑ Green Algae            ~150 mg/L

Considering that it is unlikely the toxic components will partition fully to the water column under most conditions, this is considered to be a conservative estimate for the overall aquatic toxicity of EP-202MP under actual conditions that might be encountered. It can be concluded that EP-202MP has a low to moderate potential for aquatic toxicity that is further moderated by the high biodegradability and chemical reactivity of the toxic components.

**Recommendation:** No additional ecotoxicity studies are recommended. The available information fills the HPV required data elements.

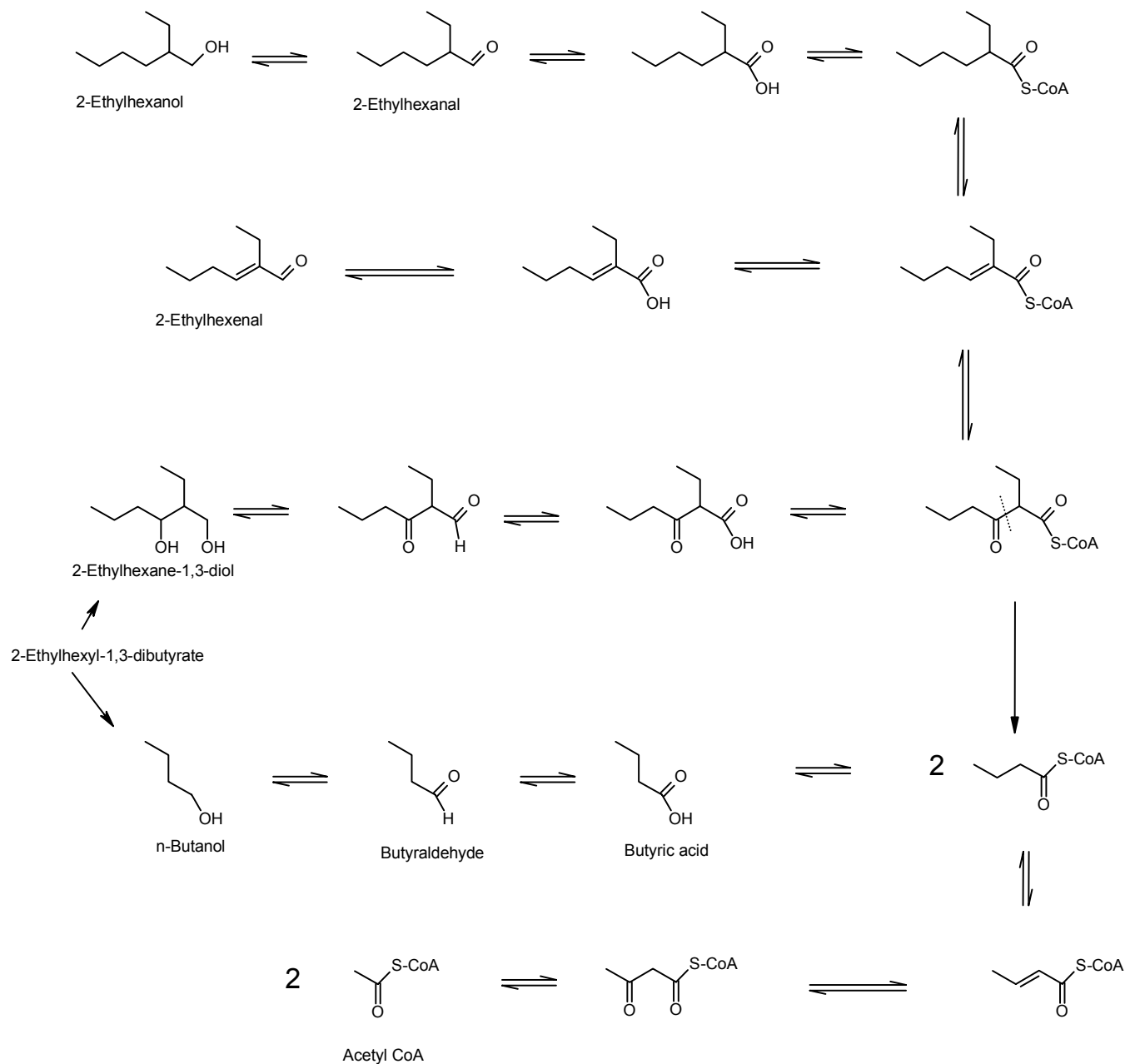
## Health Effects

An acute oral study has been conducted on EP-202MP showing low acute toxicity. Several studies have been conducted on components of EP-202MP; these cover repeat dose and developmental toxicity of various components. The most relevant component is considered to be 2-ethylhexanol because of its metabolic link to most of the C8 compounds and even to some of the C4 compounds.

## Metabolic Considerations

If one examines the spectrum of components in EP-202MP and considers the expected metabolic fate of each component, it becomes apparent that there metabolic relationships and/or potential biochemical pathways connecting many of the major components. Figure 3 presents a depiction of some of the possible biochemical connections of the EP-202MP components. While it is known that 2-ethylhexanol is extensively oxidatively metabolized, only the metabolites on the first line are definitively known to be in the 2-ethylhexanol metabolic pathway by virtue of the demonstrated urinary excretion of 2-ethylhexanoic acid (21). Nevertheless, these are all known pathways.

Considering the common pathways, it is a reasonable approach to use data from 2-ethylhexanol as a surrogate for systemic health effects from EP-202MP. Any “point of contact” effects that might be associated with administration of a reactive material, such as an aldehyde, would be excluded from this surrogate approach but for systemic toxicities (e.g. developmental effects), 2-ethylhexanol would appear to be a reasonable surrogate on metabolic grounds.



**Figure 3. Putative Metabolic Interconversions of EP-202MP Components**

## Acute Toxicity

### Oral Exposure

The oral LD<sub>50</sub> of EP-202MP (tested as the butanol distillation heavy fraction, known as Oxooel 740<sup>i</sup>) was determined to be greater than 5,000 mg/kg in Wistar rats of each sex. In this guideline study, Wistar rats were dosed at 2000 or 5000 mg/kg and observed for 14 days. Only one high-dose male died. High-dose males showed clinical signs of intoxication more strongly than females. No specific target organ was identified (22).

### Inhalation Exposure

A subchronic inhalation study using essentially saturation concentrations of 2-ethylhexanol vapors (120 ppm) has been conducted with no mortality after 13-weeks of exposure for 6 hours a day (30).

The aldehyde components are potentially inhalation hazards but they are such strong respiratory irritants that significant exposure of workers is considered unlikely (23).

### Dermal Exposure

Dermally administered 2-ethylhexanol was evaluated for developmental toxicity using three groups of 25 pregnant female Fischer 344 rats that were treated cutaneously with 2-ethylhexanol at dose levels of 0, 0.3, 1.0, or 3.0 ml/kg-day (0, 250, 830 or 2,500 mg/kg-day) for 6 hours per day on gestation days 6 through 15 (24). No maternal deaths occurred but some maternal toxicity was apparent in that maternal weight gain was significantly reduced during gestation day 6 through 9 in the high-dose animals.

The dermal LD<sub>50</sub> of 2-ethylhexanal (123–05–7) has been determined to be 5040 mg/kg in rabbits (25) and greater than 20,000 mg/kg for guinea pigs (26). As this material is one of the major components of EP-202MP and a member of the aldehyde family (which is considered to be the category of materials most likely responsible for any toxic effects of EP-202MP), this information reduces concern for the dermal hazard of EP-202MP.

Butyraldehyde, another component of concern for dermal toxicity due to its lower molecular weight and moderate K<sub>o/w</sub>, has been found to be relatively nontoxic by skin administration. Skog found the dermal LD<sub>50</sub> of butyraldehyde to be greater than 20,000 mg/kg for guinea pigs (27).

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<sup>i</sup> Oxooel 740 is the BASF designation for the heavy fraction from the distillation of the butanols. It was referred to as ‘Residue-B’ earlier in this document and it is considered to have a very similar composition to “Residue-A”. Residue-B (Oxooel 740) comprises approximately 30% of EP-202MP.

**Recommendation:** No additional acute toxicity studies are recommended. The available data fill the HPV required endpoints for acute toxicity. Although not all of the available studies meet the requirements of the current OECD guidelines, the weight of evidence shows that the oral and inhalation toxicity is very low. Likewise, the limited study of dermal toxicity provides support for low hazard by this route. Conduct of additional studies would not add significantly to our understanding of this material's toxicity and it is recommended that no additional acute toxicity studies be conducted.

## Repeat Dose Toxicity

### Oral Exposure

Repeated dose studies are available for a few of the components of EP-202MP; however, because of the metabolic commonality of probably pathways, 2-ethylhexanol was selected as the surrogate chemical of choice for assessing potential repeated dose toxicity of EP-202MP.

Recently conducted 13-week (28) and 2-year (29) studies are available for 2-ethylhexanol by oral gavage. In the 13-week study, groups of 10 rats of each sex received daily oral gavage doses of 0, 25, 125, 250 or 500 mg/kg on 5 consecutive days per week for 13 weeks. Peroxisome proliferation was also determined in satellite groups of animals. The 500-mg/kg dose was associated with significant peroxisome proliferation and systemic toxicity as evidenced by small but statistically significant ( $p < 0.01$ ) reduction in weight gain in rats of each sex. Target organs were the liver and forestomach. There was a slight increase in relative testis weight at 500 mg/kg but this was not correlated with any morphological changes. Reduced relative ovarian weight was seen at 250 mg/kg but did not occur at 500 mg/kg and there was no morphological correlate; thus, it is considered incidental. It is concluded that 125 mg/kg was a NOAEL based on organ weight changes at 250 mg/kg. The primary "adverse" effect was peroxisome proliferation. Results of the 2-year study were similar in that gavage dosing of 500 mg/kg to rats was found to be associated with increased mortality (52%), liver lesions, and increase in relative testis weight. 2-Ethylhexanol was not considered carcinogenic. Significant increases in stomach, kidney and brain relative weights were observed in male rats at 150 mg/kg 2-ethylhexanol. Female rats had significantly increased stomach, liver, kidney and brain relative weights at the 150 and 500 mg/kg doses without histopathological changes. The 50-mg/kg dose level was a NOAEL.

A 90-day subchronic inhalation study of 2-ethylhexanol has also been recently published (30). This study was performed on Wistar rats in accordance with OECD testing guidelines. Groups of 10 rats of each sex were exposed to 2-ethylhexanol vapor at concentrations of 15, 40 and 120 ppm (saturated vapor at 20° C) for 6 hours/day for 90 days. Controls were exposed to air under the same conditions. No substance-related adverse effects were observed for body weight, body weight gain, mortality, organ weights, clinical biochemistry and hematological parameters including clotting time. Cyanide-insensitive palmitoyl-CoA oxidation, a marker for peroxisome proliferation, was not elevated in this study. There were no findings related to the treatment with 2-

ethylhexanol either at necropsy or at histological examination. The highest concentration tested under these conditions (120 ppm) was found to be the NOAEL for rats of each sex.

Some repeated-dose testing has been conducted on other major components. An OECD 412 Guideline inhalation study using Fisher rats has been conducted on 2-ethylhexanal but the available information is not sufficient to draw firm conclusions (31). What is available is that 250 ppm 6 h/day for 28 days was a LOAEL associated with reduction in weight gain and increased testes weights but few other effects. The NOAEL appears to be 100 ppm.

Several repeated dose studies have been conducted on n-butanol (32). Details are sparse but it would appear that n-butanol is not excessively toxic by inhalation after repeated doses and would contribute little to the toxicity of EP-202MP.

**Recommendation:** No additional repeated-dose studies are recommended. The available inhalation study adequately fills the HPV required data element for repeated-dose toxicity.

## Genetic Toxicity

The SIDS/HPV requirement for genetic toxicity screening is for two end-points, one sensitive to point mutation and one sensitive to chromosomal aberrations. In the case of this material, adequate tests have been conducted on several components of the mixture (indicating low genotoxic hazard) but not on the mixture as a whole.

### Genetic Toxicology in vitro

The prime surrogate, 2-ethylhexanol has undergone extensive genotoxicity testing with uniformly negative results. Some of these studies are listed in Table 10. Robust summaries for an Ames test (HPV mutation endpoint) and a chromosome aberration test (HPV chromosome damage endpoint) were prepared and are presented in the appendix. These were selected as representative studies based on high reliability scores for the studies and the availability of data for review and summarization.

Component	Test System	Result	Ref
2-Ethylhexanol	Ames Test [RS]	neg	33
	Ames Tests (multiple)	neg	34, 35, 36, & others
	In vitro CA [RS]	neg	33
	In vitro SCE	neg	33
	HGPRT assay (CHO cells)	neg	37
	Mouse lymphoma assay	neg	38
	Mouse micronucleus (in vivo)	neg	39
	Many others	neg	40
2-Ethylhexenal	Ames test	neg	41, 42
2-Ethylhexanal	Ames test	neg	43
n-Butanol	Ames test (multiple)	neg	44, 45
	CA in human lymphocytes	neg	46
	SCE (multiple)	neg	47, 48
	Mouse micronucleus (in vivo)	neg	49
Butyraldehyde	Ames test (multiple)	neg	50, 51, 52, 53
	CA in CHO cells	neg	54
	HGPRT	pos	55
	SCE in CHO cells	pos	54
	SCE in human lymphocytes	neg	56
	Drosophila SLRL test	neg	57, 58

**Table 10. Genotoxicity of EP-202MP Components**

Most of the available data on the major components that have obtainable data are summarized in Table 10. The materials without data are the esters and the dioxane, which are compounds that do not have any structural alerts that would suggest genotoxic activity. The aldehydes and the  $\alpha$ ,  $\beta$ -unsaturated compound 2-ethylhexenal, which are of the most concern relative to potential genotoxicity from an SAR perspective, have negative genotoxicity test data with the exception of a few positive results having been reported for butyraldehyde. Even for butyraldehyde, the weight of the evidence, when taken as a whole, indicates little genotoxic hazard. The minor identified components (i.e., < 1%) are basically of similar structures and there is no reason to anticipate any genotoxicity activity from the minor identified components. The carbon-13 NMR analysis also indicates the unidentified components have similar structural characteristics and are therefore considered to represent a low genotoxic hazard. In summary, it is concluded that EP-202MP has minimal genotoxic hazard *in vitro*.

### Genetic Toxicology in vivo

Some *in vivo* genotoxicity studies have been conducted on the components of EP-202MP and representative results are shown in Table 10. The *in vivo* studies support the *in vitro* data indicating a minimal genotoxic hazard for EP-202MP.

**Recommendation:** The SIDS requirement for genetic testing has been met for both point mutation and clastogenic effects via the data summarized in Table 10. No additional testing is recommended for this variable complex mixture.

### Reproductive Toxicity

Although no studies of the EP-202MP product have been conducted, some of the components have been evaluated and found to have little capacity to produce specific reproductive toxicity. As is the case for most of the health effects studies of EP-202MP, 2-ethylhexanol is considered to be an adequate surrogate for this mixture.

A formal reproductive toxicity study of 2-ethylhexanol was not found however there are modern 13-week and chronic studies in which the reproductive organs were evaluated and, aside from an increase in relative testes weights at high doses without corresponding histopathological changes, there were no effects on reproductive organs at the highest dose tested (500 mg/kg)(see repeat dose toxicity). In addition to this evaluation there is a negative developmental toxicity study in mice (see developmental toxicity section). This combination of lack of effects on reproductive organs combined with a modern developmental toxicity study indicating no developmental effects fulfills the HPV reproductive toxicity endpoint.

Another surrogate chemical for use in assessing the reproductive toxicity of 2-ethylhexanol and thus EP-202MP is diethylhexyl adipate (DEHA, the diester of adipic acid with 2-ethylhexanol). DEHA is known to be well absorbed by rodents and primates and rapidly converted (both in the gut and after systemic absorption) to 2-ethylhexanol (59). In a one-generation reproductive study (60), groups of Wistar-derived rats (15 males/dose; 30 females/dose) were administered DEHA in their diets at the same levels (0, 28, 170, or 1080 mg/kg/day). After 10 weeks on the diet, the animals were mated to produce one-generation of offspring that was reared to day 36 post partum. Test substance was administered continuously throughout the study (approximately 18-19 weeks of exposure). No effects were seen on male or female fertility. At the highest dose, however, there was a reduction in the body weight gain of the dams during gestation; an increase in liver weight in both male and female parents; and reductions in offspring weight gain, total litter weight, and litter size. The NOAEL and LOAEL for this study were also 170 and 1080 mg/kg/day, respectively. In summary, DEHA administration to male and female rats did not interfere with fertility even at parentally toxic doses.

Reproductive effects have been adequately assessed through the combination of the negative reproductive and developmental toxicity studies on components of this complex mixture and the subchronic study. In addition a fertility study on diethylhexyl adipate has been conducted demonstrating lack of effects on reproductive function in the rat.

**Recommendation:** No additional reproductive testing is recommended.

## Developmental Toxicity

Developmental toxicity studies of 2-ethylhexanol have been conducted for the purpose of safety evaluation. In addition, di-2-ethylhexyladipate, which is also an excellent surrogate for EP-202MP, has been evaluated for developmental toxicity.

The National Toxicology Program conducted a developmental toxicity study on 2-ethylhexanol in mice (61, 62). In this study, groups of 28 pregnant Swiss (CD-1) mice were treated with 2-ethylhexanol (2EH) in feed at 0, 90, 300 or 900 ppm in feed (corresponding to 0, 17, 60 or 194 mg/kg-day) in microencapsulated form. At sacrifice on gestational-day 17, the number of ovarian corpora lutea and uterine implantation sites, including resorptions, and dead or live fetuses, were recorded. Live and dead fetuses were weighed. Live fetuses were sexed and examined for external, visceral and skeletal malformations and variations. No adverse effects on development were reported; however, no maternal toxicity was observed. The NOAEL for developmental toxicity was 194 mg/kg-day

Dermally administered 2-ethylhexanol was evaluated for developmental toxicity using three groups of 25 pregnant female Fischer 344 rats that were dermally treated with 2-ethylhexanol at dose levels of 0, 0.3, 1.0, or 3.0 ml/kg/day (0, 250, 830 or 2,500 mg/kg-day) for 6 hours per day on gestation days 6 through 15 (63). No treatment-related maternal deaths or early pregnancy loss were seen in the treatment groups, but maternal weight gain was significantly reduced during gestation day 6 through 9 in the high-dose animals. Exfoliation and crusting were seen at treatment sites at all dose levels and erythema at dose levels 1.0 and 3.0 ml/kg-day. Low-dose groups, showed an increase in post-implantation loss, decreased litter size, and reduced fetal body weights but this was not observed in the high-dose group. There were no significant increases in incidence of malformations in the 2-ethylhexanol group relative to the sham treatment group. It can be concluded that 2-ethylhexanol has no activity as a developmental toxin by the dermal route in rats.

As discussed earlier (vide ante) another surrogate chemical for use in assessing the toxicity of EP-202MP diethylhexyl adipate (DEHA, the diester of adipic acid with 2-ethylhexanol) has been evaluated for developmental toxicity. DEHA is rapidly absorbed by rodents and converted to 2-ethylhexanol (64). In a one-generation reproductive study (65), groups of Wistar-derived rats (15 males/dose; 30 females/dose) were administered DEHA in their diets (0, 28, 170, or 1080 mg/kg-day corresponding to 0, 19, 118 or 747 mg/kg-day 2-EH). After 10 weeks on the diet, the animals were mated to produce one-generation of offspring that was reared to day-36

post partum. Test substance was administered continuously throughout the study (approximately 18-19 weeks of exposure). No effects were seen on male or female fertility. At the highest dose, however, there was a reduction in the body weight gain of the dams during gestation; an increase in liver weight in both male and female parents; and reductions in offspring weight gain, total litter weight, and litter size. In summary, DEHA administration to pregnant female rats at maternally toxic doses was associated with only minor manifestations of fetal toxicity. The developmental and maternal NOAEL was 170 mg/kg-day.

**Recommendation:** No additional developmental toxicity testing is required as the available data are sufficient to assess the developmental toxicity of this material.

## Conclusions

With regard to the parameters specified in the EPA HPV Challenge program, it is concluded that available information on EP-202MP and/or its components fills all of the requirements for physicochemical parameters, fate information, aquatic toxicity and mammalian toxicity. Although all available studies do not meet all the requirements of the current OECD guidelines, taken together the information provides a reliable hazard assessment for this variable mixture. In addition, the potential for exposure of this material to man and the environment is very limited due to its production at only one U.S site in closed systems, low volatility, few applications (*i.e.*, use primarily limited to fuel value) and good warning properties. The possibility of human exposure is considered to be limited to minor dermal exposure to this low toxicity variable mixture of chemicals.

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# HPV Program

## Data Set

**Existing Chemical Memo** : ID: 68551-11-1  
: A complex combination of products produced by the distillation of products from the hydrogenation of butanal from the hydroformylation of propene. It consists predominantly of organic compounds such as aldehydes, alcohols, esters, ethers a

**CAS No.** : 68551-11-1  
**EINECS Name** : 1-Propene, hydroformylation products, high-boiling  
**EC No.** : 271-363-2  
**TSCA Name** : 1-Propene, hydroformylation products, high-boiling

**Producer related part**

**Company** : BASF Corporation  
**Creation date** : 29.12.2003

**Status** :  
**Memo** : Prepared by:  
Toxicology and Regulatory Affairs  
Freeburg IL 62243  
rauckman@toxicsolutions.com

**Printing date** : 07.06.2004  
**Revision date** :  
**Date of last update** : 07.06.2004

**Number of pages** : 30

**Chapter (profile)** : Chapter: 1.0.1, 1.2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6.1, 3.1.1, 3.1.2, 3.3.1, 3.3.2, 3.5, 4.1, 4.2, 4.3, 4.4, 5.1.1, 5.1.2, 5.1.3, 5.1.4, 5.4, 5.5, 5.6, 5.7, 5.8.1, 5.8.2

**Reliability (profile)** : Reliability: without reliability, 1, 2, 3, 4  
**Flags (profile)** : Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

**2.1 MELTING POINT**

**Value** : ca. -90 °C

**Method** :  
This value is approximate and was derived experimentally at the manufacturing plant using a standard method.

**Remark** :  
As this material is a variable mixture this must be considered as only an approximation of the actual freezing point for any batch.

**Test substance** :  
EP-202 (CASNO 68551-11-1)

**Reliability** : (2) valid with restrictions

**Flag** : Critical study for SIDS endpoint

02.01.2004

**2.2 BOILING POINT**

**Value** : ca. 155 - 250 °C at 1013 hPa

**Method** :  
This value is approximate and was derived experimentally at the manufacturing plant using a standard method.

**Remark** :  
As this material is a variable mixture this must be considered as only an approximation of the boiling point for any batch.

**Test substance** :  
EP-202 (CASNO 68551-11-1)

**Reliability** : (2) valid with restrictions

**Flag** : Critical study for SIDS endpoint

02.01.2004

**2.4 VAPOUR PRESSURE**

**Value** : ca. 1.3 hPa at 25 °C

**Decomposition** :

**Method** : other (calculated)

**Year** :

**GLP** :

**Test substance** :

**Method** :  
The vapor pressure for the mixture is estimated using the mean of the Antoine & Grain methods as calculated using the MPBPWIN v1.40 program found in EPIWIN 3.05. The initial boiling point and the final boiling point are the only input parameters this estimate is based upon, as the program is insensitive to structure, using a determined boiling point as an input provides an estimate of the VP. Likewise the program is insensitive to melting point when calculating VPs for liquids.

The structure for 2-ethylhexanol was entered to provide a reference value

**Result**

for one of the pure major components.

As this is a variable mixture, the initial and final boiling point values are also variable.

: Experimental Database Structure Match:  
Name : 2-ETHYL-1-HEXANOL  
CAS Num : 000104-76-7  
Exp MP (deg C): -70  
Exp BP (deg C): 184.6  
Exp VP (mm Hg): 1.36E-01  
Exp VP (deg C): 25  
Exp VP ref : DAUBERT,TE & DANNER,RP (1985)

SMILES : CCCCC(CC)CO  
CHEM : EP-202  
MOL FOR: C8 H18 O1  
MOL WT : 130.23

++++++BASED ON INITIAL BP OF 155 deg C

----- SUMMARY MPBPWIN v1.40 -----

Boiling Point: 188.52 deg C (Adapted Stein and Brown Method)

Melting Point: -47.42 deg C (Adapted Joback Method)  
Melting Point: -3.59 deg C (Gold and Ogle Method)  
Mean Melt Pt : -25.50 deg C (Joback; Gold,Ogle Methods)  
Selected MP: -25.50 deg C (Mean Value)

Vapor Pressure Estimations (25 deg C):  
(Using BP: 155.00 deg C (user entered))  
(MP not used for liquids)  
VP: 1.13 mm Hg (Antoine Method)  
VP: 0.912 mm Hg (Modified Grain Method)  
VP: 4.26 mm Hg (Mackay Method)  
Selected VP: 1.02 mm Hg (Mean of Antoine & Grain methods)

+++++++ BASED ON FINAL BP OF 250 dec C

----- SUMMARY MPBPWIN v1.40 -----

Boiling Point: 188.52 deg C (Adapted Stein and Brown Method)

Melting Point: -47.42 deg C (Adapted Joback Method)  
Melting Point: -3.59 deg C (Gold and Ogle Method)  
Mean Melt Pt : -25.50 deg C (Joback; Gold,Ogle Methods)  
Selected MP: -25.50 deg C (Mean Value)

Vapor Pressure Estimations (25 deg C):  
(Using BP: 250.00 deg C (user entered))  
(MP not used for liquids)  
VP: 0.00334 mm Hg (Antoine Method)  
VP: 0.00316 mm Hg (Modified Grain Method)  
VP: 0.047 mm Hg (Mackay Method)  
Selected VP: 0.00325 mm Hg (Mean of Antoine & Grain methods)

**Test substance**

:

## 2. Physico-Chemical Data

Id 68551-11-1

Date 07.06.2004

**Conclusion** EP-202 (CASNO 68551-11-1)

The calculated vapor pressure for this mixture, assuming it is a pure material of boiling point 122 deg C, is approximately 1 mm Hg. As this is a variable mixture, a specific VP cannot be stated. It is concluded that giving the VP as a range of 1 to 5 hPa is a conservative, yet realistic estimate.

**Reliability** : (2) valid with restrictions

**Flag** : Estimates using an acceptable method are assigned a reliability score of 2.  
29.12.2003 : Critical study for SIDS endpoint (1) (2)

### 2.5 PARTITION COEFFICIENT

**Partition coefficient** : octanol-water  
**Log pow** : at °C  
**pH value** :

**Method** : Octanol water partition coefficients for the major components of EP-202 were obtained through the KOWWIN program (v1.66) by entering the structure of the component into the program using the SMILES code. These codes are listed in the results section. Where there was an experimental value found in the database associated with the program, that value was accepted. Where an experimental value was not found the program estimate was accepted.

**Result** : KOWWIN Program (v1.66) Results:  
=====

SMILES : CCCC=C(CC)C=O  
CHEM : 2-Ethylhexenal  
MOL FOR: C8 H14 O1  
MOL WT : 126.20  
Log Kow(version 1.66 estimate): 2.62

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	-CH3 [aliphatic carbon]	0.5473	1.0946
Frag	3	-CH2- [aliphatic carbon]	0.4911	1.4733
Frag	2	=CH- or =C< [olefinic carbon]	0.3836	0.7672
Frag	1	-CHO [aldehyde, aliphatic attach]	-0.9422	-0.9422
Const		Equation Constant		0.2290

Log Kow = 2.6219

SMILES : CCCCC(CC)C=O  
CHEM : 2-Ethylhexanal  
MOL FOR: C8 H16 O1  
MOL WT : 128.22  
Log Kow(version 1.66 estimate): 2.71

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	-CH3 [aliphatic carbon]	0.5473	1.0946
Frag	4	-CH2- [aliphatic carbon]	0.4911	1.9644
Frag	1	-CH [aliphatic carbon]	0.3614	0.3614
Frag	1	-CHO [aldehyde, aliphatic attach]	-0.9422	-0.9422
Const		Equation Constant		0.2290

Log Kow = 2.7072

## 2. Physico-Chemical Data

Id 68551-11-1

Date 07.06.2004

SMILES : CCCCC  
CHEM : n-Butanol  
MOL FOR: C4 H10 O1  
MOL WT : 74.12  
Log Kow(version 1.66 estimate): 0.84

### Experimental Database Structure Match:

Name : 1-Butanol  
CAS Num : 000071-36-3  
Exp Log P: 0.88  
Exp Ref : Hansch,C et al. (1995)

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	-CH3 [aliphatic carbon]	0.5473	0.5473
Frag	3	-CH2- [aliphatic carbon]	0.4911	1.4733
Frag	1	-OH [hydroxy, aliphatic attach]	-1.4086	-1.4086
Const		Equation Constant		0.2290

Log Kow = 0.8410

SMILES : CCCC(O)C(CC)CO  
CHEM : 2-Ethyl-1,3-hexanediol  
MOL FOR: C8 H18 O2  
MOL WT : 146.23  
Log Kow(version 1.66 estimate): 1.60

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	-CH3 [aliphatic carbon]	0.5473	1.0946
Frag	4	-CH2- [aliphatic carbon]	0.4911	1.9644
Frag	2	-CH [aliphatic carbon]	0.3614	0.7228
Frag	2	-OH [hydroxy, aliphatic attach]	-1.4086	-2.8172
Factor	1	Multi-alcohol correction	0.4064	0.4064
Const		Equation Constant		0.2290

Log Kow = 1.6000

SMILES : CCCC(OC(=O)CCC)C(CC)COC(=O)CCC  
CHEM : 2-Ethylhexyl-1,3-dibutyrate  
MOL FOR: C16 H30 O4  
MOL WT : 286.42  
Log Kow(version 1.66 estimate): 5.17

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	4	-CH3 [aliphatic carbon]	0.5473	2.1892
Frag	8	-CH2- [aliphatic carbon]	0.4911	3.9288
Frag	2	-CH [aliphatic carbon]	0.3614	0.7228
Frag	2	-C(=O)O [ester, aliphatic attach]	-0.9505	-1.9010
Const		Equation Constant		0.2290

Log Kow = 5.1688

SMILES : CCCC(=O)OCCCC  
CHEM : N-butyl-n-butyrate  
MOL FOR: C8 H16 O2  
MOL WT : 144.22  
Log Kow(version 1.66 estimate): 2.83

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	-CH3 [aliphatic carbon]	0.5473	1.0946
Frag	5	-CH2- [aliphatic carbon]	0.4911	2.4555
Frag	1	-C(=O)O [ester, aliphatic attach]	-0.9505	-0.9505
Const		Equation Constant		0.2290

Log Kow = 2.8286

## 2. Physico-Chemical Data

Id 68551-11-1

Date 07.06.2004

SMILES : CCCC=O  
CHEM : N-butyraldehyde  
MOL FOR: C4 H8 O1  
MOL WT : 72.11  
Log Kow(version 1.66 estimate): 0.82

### Experimental Database Structure Match:

Name : Butyraldehyde  
CAS Num : 000123-72-8  
Exp Log P: 0.88  
Exp Ref : Hansch,C et al. (1995)

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	-CH3 [aliphatic carbon]	0.5473	0.5473
Frag	2	-CH2- [aliphatic carbon]	0.4911	0.9822
Frag	1	-CHO [aldehyde, aliphatic attach]	-0.9422	-0.9422
Const		Equation Constant		0.2290

Log Kow = 0.8163

SMILES : C1(CCC)C(CC)COC(CCC)O1  
CHEM : 2,4-Dipropyl-5-ethyl-1,3-dioxane  
MOL FOR: C12 H24 O2  
MOL WT : 200.32  
Log Kow(version 1.66 estimate): 3.89

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	3	-CH3 [aliphatic carbon]	0.5473	1.6419
Frag	6	-CH2- [aliphatic carbon]	0.4911	2.9466
Frag	3	-CH [aliphatic carbon]	0.3614	1.0842
Frag	2	-O- [oxygen, aliphatic attach]	-1.2566	-2.5132
Factor	1	C-O-C-O-C structure correction	0.5036	0.5036
Const		Equation Constant		0.2290

Log Kow = 3.8921

SMILES : CCCCC(CC)CO  
CHEM : 2-Ethylhexanol  
MOL FOR: C8 H18 O1  
MOL WT : 130.23  
Log Kow(version 1.66 estimate): 2.73

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	-CH3 [aliphatic carbon]	0.5473	1.0946
Frag	5	-CH2- [aliphatic carbon]	0.4911	2.4555
Frag	1	-CH [aliphatic carbon]	0.3614	0.3614
Frag	1	-OH [hydroxy, aliphatic attach]	-1.4086	-1.4086
Const		Equation Constant		0.2290

Log Kow = 2.7319

### Test substance

: Components of EP-202

### Conclusion

: The following values were found for log Kow

**COMPONENT*****	**log Kow**
2-Ethylhexenal	2.62 c
2-Ethylhexanal	2.71 c
N-butanol	0.88 e
2-Ethyl-1,3-hexanediol	1.60 c
2-Ethylhexyl-1,3-dibutyrate	5.17 c
N-butyl-n-butyrate	2.83 c
N-butyraldehyde	-0.48 e
2,4-Dipropyl-5-ethyl-1,3-dioxane	3.89 c
2-Ethylhexanol	2.73 c

e = experimental  
c = calculated

### Reliability

: (2) valid with restrictions

Estimates using an acceptable method are assigned a reliability score of 2.

### Flag

: Critical study for SIDS endpoint

02.01.2004

(3)

## 2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water  
 Value : at °C  
 pH value :  
 concentration : at °C  
 Temperature effects :  
 Examine different pol. :  
 pKa : at 25 °C  
 Description :  
 Stable :

## Method

: Water solubility estimates and experimental values for the major components of EP-202 were obtained through the WSKOW program (v1.40) by entering the structure of the component into the program using the SMILES code. These codes are listed in the results section. Where there was an experimental value found in the database associated with the program, that value was accepted. Where an experimental value was not found the program estimate was accepted.

The following formula was used by the program to estimate the water solubility:

$$\text{Log S (mol/L)} = 0.796 - 0.854 \log \text{Kow} - 0.00728 \text{ MW} + \text{Correction}$$

The only Correction Value that was applied was for the two non-diol aliphatic alcohols.

Alcohol, aliphatic 0.510

## Result

: The following results were obtained for water solubility:

***COMPONENT***	**SMILES**	Water Sol (mg/L)
2-Ethylhexenal	CCCC=C(CC)C=O	586 e
2-Ethylhexanal	CCCCC(CC)C=O	108 c
n-Butanol	CCCCO	6320 e
2-Ethyl-1,3-hexanediol	CCCC(O)C(CC)CO	4200 e
2-Ethylhexyl-1,3-dibutyrate	CCCC(OC(=O)CCC)C(CC)COC(=O)CCC	0.56 c
n-Butyl-n-butyrate	CCCC(=O)OCCCC	309 c
n-Butyraldehyde	CCCC=O	238 e
2,4-Dipropyl-5-ethyl-1,3-dioxane	C(CCC)1C(CC)COC(CCC)O1	20.7 c
2-Ethylhexanol	CCCCC(CC)CO	880 e

e = experimental  
 c = calculated

## Test substance

: Components of EP-202

## Conclusion

: Water solubility varies for components of EP-202 from less than 1 mg/L to 6800 mg/L.

## Reliability

: (2) valid with restrictions

## Flag

02.01.2004

: Estimates using an acceptable method are assigned a reliability score of 2.  
 Critical study for SIDS endpoint

(4)

## 3.1.1 PHOTODEGRADATION

Type : air  
Light source :  
Light spectrum : nm  
Relative intensity : based on intensity of sunlight

Test substance : Components of EP-202  
31.12.2003

## 3.1.2 STABILITY IN WATER

Type : abiotic  
t1/2 pH4 : at °C  
t1/2 pH7 : at °C  
t1/2 pH9 : at °C

Method : Water stability is estimated using chemical principles and HYDROWIN modeling.

Most of the components do not contain a water-reactive or hydrolysable group. The following are considered water stable\* for this reason:

Aliphatic alcohols  
Aliphatic ethers

The materials that are potentially hydrolysable are;  
Aliphatic esters

These were entered into EPIWIN (HYDROWIN v1.67) to estimate hydrolysis rates using the following SMILES notations

Ref: J.C. Harris. Rate of Hydrolysis' in Handbook of Chemical Property Estimation Methods, WJ Lyman ed. ACS publication 1990.

Result : The following results were obtained for water stability:

HYDROWIN Program (v1.67) Results:

=====

```
SMILES : CCCC(OC(=O)CCC)C(CC)COC(=O)CCC
CHEM   : 2-Ethylhexyl-1,3-dibutyrate
MOL FOR: C16 H30 O4
MOL WT : 286.42
```

----- HYDROWIN v1.67 Results -----

NOTE: Fragment(s) on this compound are NOT available from the fragment library. Substitute(s) have been used!!! Substitute R1, R2, R3, or R4 fragments are marked with double asterisks "\*\*\*".

```
ESTER:  R1-C(=O)-O-R2                      R1: n-Propyl-
** R2:  -CH(Me)(t-Bu)
Kb hydrolysis at atom # 6:  1.455E-003  L/mol-sec
```

```
ESTER:  R1-C(=O)-O-R2                      R1: n-Propyl-
** R2:  iso-Butyl-
```

Kb hydrolysis at atom # 16: 3.416E-002 L/mol-sec

Total Kb for pH > 8 at 25 deg C : 3.561E-002 L/mol-sec  
Kb Half-Life at pH 8: 225.252 days  
Kb Half-Life at pH 7: 6.167 years

### 3. Environmental Fate and Pathways

Id 68551-11-1

Date 07.06.2004

SMILES : CCCC(=O)OCCCC  
CHEM : N-butyl-n-butyrate  
MOL FOR: C8 H16 O2  
MOL WT : 144.22  
----- HYDROWIN v1.67 Results -----

ESTER: R1-C(=O)-O-R2 R1: n-Propyl-  
R2: n-Butyl-  
Kb hydrolysis at atom # 4: 5.317E-002 L/mol-sec  
Total Kb for pH > 8 at 25 deg C : 5.317E-002 L/mol-sec  
Kb Half-Life at pH 8: 150.863 days  
Kb Half-Life at pH 7: 4.130 years

Test substance

:

Components of EP-202

Conclusion

:

Most components do not have a hydrolysable group and are considered stable, the two esters will be slowly hydrolyzed with estimated half-lives of greater than 1 year at pH 7.

Estimated Kb and half-live values are:

	Kb L/mol-s	half-life (yr)	
		pH 7	pH 8
2-Ethylhexenal	0	>> 1	> 1
2-Ethylhexanal	0	>> 1	> 1
n-Butanol	0	>> 1	> 1
2-Ethyl-1,3-hexanediol	0	>> 1	> 1
2-Ethylhexyl-1,3-dibutyrate	0.0015	6.2	0.62
n-Butyl-n-butyrate	0.053	4.1	0.41
n-Butyraldehyde	0	>> 1	> 1
2,4-Dipropyl-5-ethyl-1,3-dioxane	0	>> 1	> 1
2-Ethylhexanol	0	>> 1	> 1

Reliability

:

(2) valid with restrictions

Flag

:

Estimates using an acceptable method are assigned a reliability score of 2.  
Critical study for SIDS endpoint

02.01.2004

(5) (6)

#### 3.3.2 DISTRIBUTION

Media

:

other: air, water, soil and sediment

Method

:

Calculation according Mackay, Level III

Year

:

Method

:

Theoretical Distribution (Fugacity) of EP-202 in the environment was estimated using the MacKay EQC level III model with standard defaults in EPIWIN v 3.05 using equal releases to water, soil and air (EPIWIN default) as the means of entry into the environment. The approach used was to take the nine materials represented in the in the preparation at greater than 1% and individually determine their fugacity assuming that one component will not greatly affect the distribution of the other. As the measured vapor pressure of EP-202 is a function of the partial pressures of each component, it is more appropriate to use the EPIWIN predicted vapor pressure for each component in the calculation. Likewise, individual predicted values for log Kow, Koc, and half-lives were utilized. The biodegradation half-lives that were utilized were EPIWIN generated but were evaluated for consistency with the known biodegradability of the preparation and found to be representative.

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**Result**

: Level III Fugacity Model (Full-Output):

=====

Chem Name : 2-Ethylhexenal  
Molecular Wt: 126.2  
Henry's LC : 0.000488 atm-m3/mole (Henrywin program)  
Vapor Press : 0.463 mm Hg (Mppwin program)  
Log Kow : 2.62 (Kowwin program)  
Soil Koc : 171 (calc by model)

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	1.39	4.21	1000
Water	34.7	360	1000
Soil	63.7	360	1000
Sediment	0.216	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	1.73e-011	1.47e+003	89.2	49	2.97
Water	4.31e-009	429	223	14.3	7.44
Soil	1.99e-008	788	0	26.3	0
Sediment	2.64e-009	0.669	0.0278	0.0223	0.000927

Persistence Time: 214 hr  
Reaction Time: 239 hr  
Advection Time: 2.06e+003 hr  
Percent Reacted: 89.6  
Percent Advected: 10.4

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):

Air: 4.207  
Water: 360  
Soil: 360  
Sediment: 1440  
Biowin estimate: 3.241 (weeks)

Advection Times (hr):

Air: 100  
Water: 1000  
Sediment: 5e+004

Level III Fugacity Model (Full-Output):

=====

Chem Name : 2-Ethylhexenal  
Molecular Wt: 128.22  
Henry's LC : 0.000759 atm-m3/mole (Henry database)  
Vapor Press : 2.18 mm Hg (Mppwin program)  
Log Kow : 2.71 (Kowwin program)  
Soil Koc : 210 (calc by model)

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	2.58	7.56	1000
Water	34.1	360	1000
Soil	63	360	1000
Sediment	0.241	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	3.05e-011	1.47e+003	160	48.9	5.33
Water	6.26e-009	408	212	13.6	7.06
Soil	2.4e-008	752	0	25.1	0
Sediment	3.66e-009	0.719	0.0299	0.024	0.000996

Persistence Time: 207 hr  
Reaction Time: 236 hr  
Advection Time: 1.67e+003 hr  
Percent Reacted: 87.6  
Percent Advected: 12.4

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):

Air: 7.555  
Water: 360  
Soil: 360  
Sediment: 1440  
Biowin estimate: 3.236 (weeks)

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#### Advection Times (hr):

Air: 100  
Water: 1000  
Sediment: 5e+004

#### Level III Fugacity Model (Full-Output):

=====

Chem Name : n-Butanol  
Molecular Wt: 74.12  
Henry's LC : 8.81e-006 atm-m3/mole (Henry database)  
Vapor Press : 7.78 mm Hg (Mppbpwin program)  
Log Kow : 0.88 (Kowwin program)  
Soil Koc : 3.11 (calc by model)

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	5.91	30	1000
Water	49.5	208	1000
Soil	44.5	208	1000
Sediment	0.0782	832	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	1.05e-010	735	317	24.5	10.6
Water	1.58e-010	886	266	29.5	8.87
Soil	4.21e-009	796	0	26.5	0
Sediment	1.16e-010	0.35	0.0084	0.0117	0.00028

Persistence Time: 179 hr  
Reaction Time: 222 hr  
Advection Time: 920 hr  
Percent Reacted: 80.5  
Percent Advected: 19.5

#### Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):

Air: 29.95  
Water: 208.1  
Soil: 208.1  
Sediment: 832.3  
Biowin estimate: 3.494 (days-weeks )

#### Advection Times (hr):

Air: 100  
Water: 1000  
Sediment: 5e+004

#### Level III Fugacity Model (Full-Output):

=====

Chem Name : 2-Ethyl-1,3-hexanediol  
Molecular Wt: 146.23  
Henry's LC : 1.37e-008 atm-m3/mole (Henry database)  
Vapor Press : 0.003 mm Hg (Mppbpwin program)  
Log Kow : 1.6 (Kowwin program)  
Soil Koc : 16.3 (calc by model)

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.34	11.5	1000
Water	38.6	360	1000
Soil	61	360	1000
Sediment	0.0859	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	6.7e-012	241	40.1	8.02	1.34
Water	2.13e-013	877	456	29.2	15.2
Soil	5.42e-012	1.39e+003	0	46.2	0
Sediment	1.71e-013	0.488	0.0203	0.0163	0.000676

Persistence Time: 394 hr  
Reaction Time: 471 hr  
Advection Time: 2.38e+003 hr  
Percent Reacted: 83.5  
Percent Advected: 16.5

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Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):

Air: 11.55  
Water: 360  
Soil: 360  
Sediment: 1440  
Biowin estimate: 3.196 (weeks )

Advection Times (hr):

Air: 100  
Water: 1000  
Sediment: 5e+004

Level III Fugacity Model (Full-Output):

=====

Chem Name : 2-Ethylhexyl-1,3-dibutyrate  
Molecular Wt: 286.42  
Henry's LC : 3.7e-006 atm-m3/mole (Henrywin program)  
Vapor Press : 0.00147 mm Hg (Mppbpwin program)  
Log Kow : 5.17 (Kowwin program)  
Soil Koc : 6.06e+004 (calc by model)

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	1.59	14.6	1000
Water	27.7	360	1000
Soil	48.5	360	1000
Sediment	22.2	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	1.47e-011	816	172	27.2	5.75
Water	1.77e-011	578	301	19.3	10
Soil	2.59e-013	1.01e+003	0	33.7	0
Sediment	5.33e-012	116	4.81	3.86	0.16

Persistence Time: 361 hr  
Reaction Time: 430 hr  
Advection Time: 2.27e+003 hr  
Percent Reacted: 84.1  
Percent Advected: 15.9

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):

Air: 14.64  
Water: 360  
Soil: 360  
Sediment: 1440  
Biowin estimate: 2.847 (weeks )

Advection Times (hr):

Air: 100  
Water: 1000  
Sediment: 5e+004

Level III Fugacity Model (Full-Output):

=====

Chem Name : N-butyl-n-butyrate  
Molecular Wt: 144.22  
Henry's LC : 0.000687 atm-m3/mole (Henry database)  
Vapor Press : 1.76 mm Hg (Mppbpwin program)  
Log Kow : 2.83 (Kowwin program)  
Soil Koc : 277 (calc by model)

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	7.8	24.2	1000
Water	35.2	208	1000
Soil	56.8	208	1000
Sediment	0.208	832	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	6.17e-011	1.04e+003	364	34.7	12.1
Water	3.91e-009	547	164	18.2	5.47
Soil	1.01e-008	883	0	29.4	0
Sediment	1.51e-009	0.808	0.0194	0.0269	0.000647

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Persistence Time: 156 hr  
Reaction Time: 189 hr  
Advection Time: 883 hr  
Percent Reacted: 82.4  
Percent Advected: 17.6

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):

Air: 24.22  
Water: 208.1  
Soil: 208.1  
Sediment: 832.3  
Biowin estimate: 3.319 (days-weeks )

Advection Times (hr):

Air: 100  
Water: 1000  
Sediment: 5e+004

Level III Fugacity Model (Full-Output):

=====

Chem Name : N-butyraldehyde  
Molecular Wt: 72.11  
Henry's LC : 0.000115 atm-m3/mole (Henry database)  
Vapor Press : 108 mm Hg (Mppbpwin program)  
Log Kow : 0.88 (Kowwin program)  
Soil Koc : 3.11 (calc by model)

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	3.68	10.9	1000
Water	53.5	360	1000
Soil	42.7	360	1000
Sediment	0.095	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	7.34e-011	1.38e+003	217	45.8	7.23
Water	2.51e-009	607	315	20.2	10.5
Soil	5.95e-008	485	0	16.2	0
Sediment	2.08e-009	0.27	0.0112	0.00898	0.000373

Persistence Time: 197 hr  
Reaction Time: 239 hr  
Advection Time: 1.11e+003 hr  
Percent Reacted: 82.3  
Percent Advected: 17.7

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):

Air: 10.92  
Water: 360  
Soil: 360  
Sediment: 1440  
Biowin estimate: 3.062 (weeks )

Advection Times (hr):

Air: 100  
Water: 1000  
Sediment: 5e+004

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#### Level III Fugacity Model (Full-Output):

=====

Chem Name : 2,4-Dipropyl-5-ethyl-1,3-dioxane  
Molecular Wt: 200.32  
Henry's LC : 0.000286 atm-m3/mole (Henrywin program)  
Vapor Press : 0.0433 mm Hg (Mpppwin program)  
Log Kow : 3.89 (Kowwin program)  
Soil Koc : 3.18e+003 (calc by model)

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.604	5.06	1000
Water	19.7	900	1000
Soil	77.6	900	1000
Sediment	2.13	3.6e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	1.2e-011	1.35e+003	98.6	45	3.29
Water	2.28e-009	247	321	8.24	10.7
Soil	1.31e-009	976	0	32.5	0
Sediment	1.61e-009	6.71	0.697	0.224	0.0232

Persistence Time: 544 hr  
Reaction Time: 633 hr  
Advection Time: 3.88e+003 hr  
Percent Reacted: 86  
Percent Advected: 14

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):

Air: 5.064  
Water: 900  
Soil: 900  
Sediment: 3600  
Biowin estimate: 2.739 (weeks-months)

Advection Times (hr):

Air: 100  
Water: 1000  
Sediment: 5e+004

#### Level III Fugacity Model (Full-Output):

=====

Chem Name : 2-Ethylhexanol  
Molecular Wt: 130.23  
Henry's LC : 2.65e-005 atm-m3/mole (Henry database)  
Vapor Press : 0.185 mm Hg (Mpppwin program)  
Log Kow : 2.73 (Kowwin program)  
Soil Koc : 220 (calc by model)

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	4.24	19.4	1000
Water	41.2	208	1000
Soil	54.3	208	1000
Sediment	0.216	832	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	4.31e-011	820	230	27.3	7.66
Water	2.27e-010	745	224	24.8	7.45
Soil	5.96e-010	981	0	32.7	0
Sediment	9.5e-011	0.977	0.0235	0.0326	0.000782

Persistence Time: 181 hr  
Reaction Time: 213 hr  
Advection Time: 1.2e+003 hr  
Percent Reacted: 84.9  
Percent Advected: 15.1

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):

Air: 19.4  
Water: 208.1  
Soil: 208.1  
Sediment: 832.3  
Biowin estimate: 3.370 (days-weeks )

Advection Times (hr):

Air: 100  
Water: 1000  
Sediment: 5e+004

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**Test substance** : Components of EP-202

**Conclusion** : The components of EP-202 distribute primarily to water and soil with little in the air or sediment except for the two esters, with n-butyl butyrate being more volatile and 2-ethylhexyl-1,3-dibutyrate distributing in sediment to a significant extent. Summary results are shown below.

	Air	Water	Soil	Sediment
2-Ethylhexenal	1.39	34.7	63.7	0.216
2-Ethylhexanal	2.58	34.1	63.0	0.241
n-Butanol	5.91	49.5	44.5	0.0782
2-Ethyl-1,3-hexanediol	0.34	38.6	61.0	0.0859
2-Ethylhexyl-1,3-dibutyrate	1.59	27.7	48.5	22.2
2,4-Dipropyl-5-ethyl-1,3-dioxane	0.604	19.7	77.6	2.13
n-Butyl-n-butyrate	7.8	35.2	56.8	0.208
n-Butyraldehyde	3.68	53.5	42.7	0.095
2-Ethylhexanol	4.24	41.2	54.3	0.216

**Reliability** : (2) valid with restrictions

**Flag** : Estimates using an acceptable method are assigned a reliability score of 2.  
03.01.2004 : Critical study for SIDS endpoint

(7)

## 4.1 ACUTE/PROLONGED TOXICITY TO FISH

<b>Type</b>	: semistatic
<b>Species</b>	: Cyprinus carpio (Fish, fresh water)
<b>Exposure period</b>	: 96 hour(s)
<b>Unit</b>	: mg/l
<b>LC0</b>	: = 3 measured/nominal
<b>LC50</b>	: = 6 measured/nominal
<b>LC100</b>	: = 12 measured/nominal
<b>Limit test</b>	: no
<b>Analytical monitoring</b>	: yes
<b>Method</b>	: Directive 84/449/EEC, C.1 "Acute toxicity for fish"
<b>Year</b>	: 1992
<b>GLP</b>	: yes
<b>Test substance</b>	: other TS
<b>Remark</b>	: Multiple aquatic studies are available for this material at all trophic levels. This study was selected as it had the lowest EC50 for fish and was conducted under GLPs.
<b>Source</b>	: IUCLID 2000 Document
<b>Test substance</b>	: 2-Ethylhexenal CASNO 645-62-5
<b>Reliability</b>	: (1) valid without restriction  Guideline study under GLPs from IUCLID 2000. Supporting studies increase reliability.
<b>Flag</b>	: Critical study for SIDS endpoint
03.01.2004	(8)
<b>Type</b>	: static
<b>Species</b>	: Salmo gairdneri (Fish, estuary, fresh water)
<b>Exposure period</b>	: 96 hour(s)
<b>Unit</b>	: mg/l
<b>LC0</b>	: = 6.3 measured/nominal
<b>LC50</b>	: = 8 measured/nominal
<b>LC100</b>	: = 10 measured/nominal
<b>Method</b>	: OECD Guide-line 203 "Fish, Acute Toxicity Test"
<b>Year</b>	: 1979
<b>GLP</b>	:
<b>Test substance</b>	: other TS
<b>Remark</b>	: Two other acute fish studies are reported for this material in IUCLID 2000 that give similar results in other species (Lepomis gibbosus, LC50 11 mg/l; Leuciscus idus. LC50 10-32 mg/L). This study selected because it has the lowest LC50.
<b>Test substance</b>	: 2-Ethylhexenal CASNO 123-05-7 purity 99%
<b>Reliability</b>	: (2) valid with restrictions  Guideline study from IUCLID 2000 without many details. Supporting studies available on same material increases reliability.
<b>Flag</b>	: Critical study for SIDS endpoint
03.01.2004	(9)

## 4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

<b>Type</b>	: other: no data
<b>Species</b>	: Daphnia magna (Crustacea)
<b>Exposure period</b>	: 48 hour(s)
<b>Unit</b>	: mg/l
<b>EC0</b>	: = 12.5 measured/nominal
<b>EC50</b>	: = 20 measured/nominal
<b>EC100</b>	: = 50 measured/nominal
<b>Limit Test</b>	: no
<b>Analytical monitoring</b>	: no data
<b>Method</b>	: Directive 84/449/EEC, C.2 "Acute toxicity for Daphnia"
<b>Year</b>	: 1984
<b>GLP</b>	: no data
<b>Test substance</b>	: other TS
<b>Remark</b>	: Multiple aquatic studies are available for this material at all trophic levels. This study was selected as it had the lowest EC50 for daphnids.
<b>Test substance</b>	: 2-Ethylhexenal CASNO 645-62-5
<b>Reliability</b>	: (2) valid with restrictions
<b>Flag</b> 03.01.2004	: Guideline study from IUCLID 2000. Supporting studies increase reliability. Critical study for SIDS endpoint (10)
<b>Type</b>	: other: no data
<b>Species</b>	: Daphnia magna (Crustacea)
<b>Exposure period</b>	: 48 hour(s)
<b>Unit</b>	: mg/l
<b>EC0</b>	: = 6.25 - 11.5 measured/nominal
<b>EC50</b>	: = measured/nominal
<b>EC100</b>	: = 25 measured/nominal
<b>Method</b>	: Directive 84/449/EEC, C.2 "Acute toxicity for Daphnia"
<b>Year</b>	:
<b>GLP</b>	: no data
<b>Test substance</b>	: other TS
<b>Remark</b>	: Only daphnia study available for chemical.
<b>Test substance</b>	: 2-Ethylhexenal CASNO 123-05-7
<b>Reliability</b>	: (2) valid with restrictions
<b>Flag</b> 03.01.2004	: Guideline study from IUCLID 2000 without many details included. Supporting studies available for similar materials increases reliability. Critical study for SIDS endpoint (11)

## 4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

<b>Species</b>	: Scenedesmus subspicatus (Algae)
<b>Endpoint</b>	: growth rate
<b>Exposure period</b>	: 72 hour(s)
<b>Unit</b>	: mg/l
<b>EC50</b>	: = 19.3 measured/nominal
<b>EC90</b>	: = 54 measured/nominal
<b>EC20</b>	: = 12.8 measured/nominal
<b>Method</b>	: other: Algentest in Anlehnung an UBA
<b>Year</b>	:
<b>GLP</b>	:
<b>Test substance</b>	: other TS
<b>Remark</b>	: Multiple aquatic studies are available for this material at all trophic levels. This study was selected as it had the lowest EC50 for green algae.
<b>Test substance</b>	: 2-Ethylhexenal CASNO 645-62-5
<b>Reliability</b>	: (2) valid with restrictions
<b>Flag</b>	: Guideline study from IUCLID 2000. Supporting studies increase reliability. Critical study for SIDS endpoint
03.01.2004	(12)
<b>Species</b>	: Scenedesmus subspicatus (Algae)
<b>Endpoint</b>	: growth rate
<b>Exposure period</b>	: 96 hour(s)
<b>Unit</b>	: mg/l
<b>EC50</b>	: = 52 measured/nominal
<b>EC20</b>	: = 36 measured/nominal
<b>EC90</b>	: = 111 measured/nominal
<b>Method</b>	: other: Scenedesmus-Zellvermehrungs-Hemmtest, DIN 38412 Teil 9, Bestimmung der Hemmwirkung von Wasserinhaltsstoffen auf Gruenalgen
<b>Year</b>	:
<b>GLP</b>	:
<b>Test substance</b>	:
<b>Remark</b>	: Only green algae study available for chemical.
<b>Test substance</b>	: 2-Ethylhexenal CASNO 123-05-7
<b>Reliability</b>	: (2) valid with restrictions
<b>Flag</b>	: Guideline study from IUCLID 2000 without many details. Supporting studies available for similar materials increases reliability. Critical study for SIDS endpoint
03.01.2004	(13)

## 5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	> 5000 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	20
Vehicle	:	other: olive oil
Doses	:	2000 or 5000 mg/kg bw
Method	:	other: Directive 83/467/EWG
Year	:	1983
GLP	:	yes
Test substance	:	
Method	:	Groups of five overnight-fasted Wistar rats were dosed at 5000 or 2000 mg/kg with test material in olive oil. After administration animals were observed for a period of 14 days, sacrificed and examined for signs of adverse effects. Animal weights (as group mean) were recorded at the beginning of the study and on days 3, 5, 7 and 13.
Remark	:	Oxooel 740 is the BASF designation for the heavy fraction from the distillation of the butanols. In Germany, the hydroformylation chemistry is practiced with slight modification and the heavy ends from the distillation of the aldehydes is not blended with the heavy ends from distillation of the alcohols. As discussed in the HPV testing plan, the chemical reactions producing the heavy fraction are essentially identical and the compositions of the US product EP-202MP and the German equivalent product Oxooel 740 are very similar, both are variable and both share the same CAS registry number. The only difference is that the EP-204MP has a slightly higher quantity of C4 compounds.
Result	:	One 5000-mg/kg male died on day 1. No other animal died on test.  Body weight gain was normal in treated females but appeared to be slightly retarded in 5000-mg/kg males.  Clinical signs of intoxication were not observed at 2000 mg/kg. At 5000 mg/kg males showed more severe signs consisting of dyspnea, apathy, atonia, staggering, piloerection, and similar signs extended to 3 days after treatment. High dose females showed similar clinical signs but to a lesser degree and they only persisted for one day.
Test substance	:	Oxooel 740 ROH (German production material corresponding with US EP-202)
Conclusion	:	The LD50 for this material in Wistar rats of each sex is > 5000 mg/kg. No target organs were identified. Males may be the more sensitive sex.
Reliability	:	(1) valid without restriction
Flag	:	Guideline study under GLPS
07.06.2004	:	Critical study for SIDS endpoint

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## 5.1.2 ACUTE INHALATION TOXICITY

## 5.1.3 ACUTE DERMAL TOXICITY

## 5.1.4 ACUTE TOXICITY, OTHER ROUTES

## 5.4 REPEATED DOSE TOXICITY

Type	: Sub-chronic
Species	: rat
Sex	: male/female
Strain	: Fischer 344
Route of admin.	: gavage
Exposure period	: 13 weeks
Frequency of treatm.	: 5 days/week
Post exposure period	: none
Doses	: 0, 25, 125, 250 or 500 mg/kg-bw
Control group	: yes, concurrent vehicle
NOAEL	: = 125 mg/kg bw
LOAEL	: = 250 mg/kg bw
Method	:
Year	:
GLP	: no data
Test substance	: other TS

**Method** :  
Animals. F344 rats, 36- to 37-days-old at delivery, were kept singly in stainless steel wire cages. Mean body weight ranges at dosing were (male) 105-114 g and (female) 86-97 g. Animals were acclimated 6 days on a 12-hr photoperiod at 20-24°C and 30-70% relative humidity; food and water were ad lib.

In the 13-week study groups of 10 animals of each sex rats received daily oral gavage doses of 0, 25, 125, 250 or 500 mg/kg on 5 consecutive days per week. Doses were prepared daily by dispersing TS in an aqueous solution of Cremophor EL (5 mg/100 ml). Dosing volume was 10 ml/kg, based on weekly body weights. Controls received 5.0 ml/kg vehicle. Concentrations and homogeneity were checked by gas chromatographic analysis of samples from each dose level at study start and periodically during the 13-week study. Animals were fasted for about 16 hr after the last dose and terminated by decapitation under CO<sub>2</sub> anesthesia.

In-life observations. Animals were inspected twice daily for morbidity and mortality but only once daily on nontreatment days. Clinical observations were made daily. Body weights were determined on day 01 and weekly thereafter. Animals were palpated on weighing. Average daily food consumption was determined weekly. Blood was collected by retroorbital bleeding from fasted animals on the morning of Days 29 and 84. Standard serum enzyme activities and biochemistry measurements were recorded. Hematology parameters were leucocytes, erythrocytes, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin,

mean corpuscular hemoglobin concentration, platelets, differential leucocytes, and reticulocytes.

Observations at necropsy. Moribund animals were euthanized and dead and euthanized animals were immediately necropsied for gross pathology. At scheduled terminations body and organ weights were measured. At study termination adrenals, brains, kidneys, livers, stomachs, testes, and ovaries from all animals were weighed, and with other organs and tissues listed in U.S. EPA Health Effects Guidelines (1987b) fixed in 4% formalin. All tissues from high dose and control animals were stained with hematoxylin-eosin and examined microscopically. Lungs, livers, spleens, kidneys, stomachs, sternums, femurs, and femur bone marrows were examined microscopically at intermediate dose levels. Skin, eyes, female mammary glands, thigh musculatures, and extraorbital lacrymatory glands were not examined in the absence of signs of toxicity. Livers were also stained with oil red for reticulolipid content and examined microscopically.

Ancillary studies were used only to determine hepatic peroxisome proliferation. Livers were removed at termination and weighed, and cyanide-insensitive pCoA activities and protein concentrations were determined.

Statistical treatment of data. Means and standard deviations were calculated for body weights, food and water consumption, clinical pathology results, and organ weights. Values for test groups were compared with controls in the main study by ANOVA followed by Dunnett's test.

**Result**

:

No rat died on test. There was decreased weight gain in male and female rats at 500 mg/kg, starting at Week 4 in males and Week 11 in females, amounting to weight losses of 7% in males and 6% in females by Week 13. There were no differences from controls at any treatment level in food consumption.

Clinical pathology. Differences from control values were seen mostly at 84 days. Females at 250 and 500 mg/kg had 30 and 36% decreases in serum ALT activities, respectively. Females at 500 mg/kg had a 16% decrease in serum cholesterol concentration and males at 500 mg/kg had 13% decreases in total protein and albumin concentrations. There was a 25% increase in reticulocyte numbers in male and female rats at 500 mg/kg.

Necropsy findings: Relative organ weights. Significant differences from controls in rats were moderate and limited to the brain, kidneys, liver, stomach, and testes at 250 and 500 mg/kg (Table 3). Male rat relative brain weights increased by 6% at 500 mg/kg, male kidney weights by 8% at 250 and 16% at 500 mg/kg, male liver weights by 8% at 250 and 29% at 500 mg/kg, male stomach weights by 11% at 500 mg/kg, and testis weights by 5.5% at 500 mg/kg. Female's kidney weights increased by 5% at 250 and 6% at 500 mg/kg, female liver weights by 8% at 250 and 15% at 500 mg/kg, and female stomach weights by 6% at 250 and 16% at 500 mg/kg.

Necropsy findings: Gross observations. Gross lesions differing from controls 500 mg/kg only. 2/10 males and 4/10 females exhibited single or multiple slightly elevated foci in the forestomach. There were no other gross findings.

Necropsy findings: Microscopic findings. Dose-related findings were limited to the forestomach and liver at 500 mg/kg. There was a generalized acanthosis of the forestomach mucosa in 1/10 males with ballooning degeneration of the epithelial wall and acanthosis of the forestomach mucosa in 2/10 males and 5/10 females.

There was a moderate decrease in hepatic peripheral lobular fatty infiltration in 4/10 males and 2/10 females and adrenal b-cell hyperplasia in 3/10 females.

Peroxisome proliferation. Hepatic peroxisome proliferation was determined in ancillary 13-week studies by measuring activity of hepatic cyanide-insensitive palmitoyl Coenzyme A in livers at termination. Increases in pCoA activity were 6.5-fold in male rats and 3.4-fold in females at 500 mg/kg, with decreases in body weight gain similar to those in the main study.

#### Relative Organ Weights at Termination (grams (SD))

Weights at other dose levels (25 and 125 mg/kg) did not differ from controls.

Males	0	250	500
Brain	0.68 (0.03)	0.70 (0.02)	0.72 (0.02)**
Kidneys	0.69 (0.02)	0.75 (0.02)**	0.81 (0.04)**
Liver	2.77 (0.11)	2.98 (0.08)**	3.57 (0.22)**
Stomach	0.57 (0.03)	0.58 (0.03)	0.63 (0.02)**
Testes	1.11 (0.05)	1.16 (0.07)	1.17 (0.06)*

Females	0	250	500
Brain	1.07 (0.03)	1.1 (0.06)	1.1 (0.04)
Kidneys	0.77 (0.02)	0.81 (0.03)*	0.82 (0.03)**
Liver	2.67 (0.11)	2.88 (0.08)**	3.07 (0.07)**
Stomach	0.71 (0.03)	0.75 (0.03)*	0.82 (0.04)**
Ovaries	0.041(0.003)	0.037(0.005)*	0.039(0.004)

\*p 0.05

\*\* p 0.01

#### Test substance

:

2-Ethylhexanol CASNO 104-76-7 (component and surrogate)  
Purity 99.8% purity by gas chromatography.

#### Conclusion

:

The 500-mg/kg dose was associated with significant peroxisome proliferation and systemic toxicity as evidenced by small but statistically significant ( $p < 0.01$ ) reduction in weight gain in rats of each sex. Target organs were the liver and forestomach. The possible testes effects were of special interest and there was a slight increase in relative testis weight at 500 mg/kg but this was not correlated with any morphological changes. The reduced relative ovarian weight at 250 mg/kg did not occur at 500 mg/kg and is considered incidental. It is concluded that 125 mg/kg was a NOEL based on organ weight changes at 250 mg/kg.

#### Reliability

:

(2) valid with restrictions

#### Flag

05.01.2004

:

Published studies are assigned a 2  
Critical study for SIDS endpoint

(15)

**5.5 GENETIC TOXICITY 'IN VITRO'**

**Type** : Bacterial reverse mutation assay  
**System of testing** : Salmonella  
**Test concentration** : Varies  
**Cycotoxic concentr.** : See Results  
**Metabolic activation** : with and without  
**Result** : negative  
**Method** : other: National Toxicology Program  
**Year** :  
**GLP** : no data  
**Test substance** : other TS

**Method**

:

As each stain of Salmonella typhimurium is genetically different, using several strains in a test increases the opportunity of detecting a mutagenic chemical. All strains of Salmonella typhimurium used for mutagenicity testing carry a defective (mutant) gene that prevents them from synthesizing the essential amino acid histidine. Mutations leading to the ability to synthesize histidine are called "back" or "reverse" mutations and the process is referred to as "reversion."

Some test protocols utilize extracts of Aroclor rat or hamster liver enzymes (S9) to promote metabolic conversion of the test chemical. This is necessary since the Salmonella bacterium does not have the mammalian metabolic capabilities.

In the Salmonella assay, a test tube containing a suspension of one strain of Salmonella typhimurium plus S9 mix or plain buffer without S9, is incubated for 20 minutes at 37° C with the test chemical. Control cultures, with all the same ingredients except the test chemical, are also identically incubated. In addition, positive controls with a known potent mutagen, are prepared. After 20 minutes, agar is added to the cultures and the contents of the tubes are thoroughly mixed and poured onto the surface of petri dishes containing standard bacterial culture medium. The plates are incubated, and bacterial colonies that do not require an excess of supplemental histidine appear and grow. These colonies are comprised of Salmonella that have undergone reverse mutation to restore function of the histidine-manufacturing gene. The number of colonies is counted after 2 days.

Several doses (at least 5) of each test chemical and multiple strains of Salmonella typhimurium are used in each experiment. In addition, cultures are set up with and without added S9 liver enzymes at 10% concentration in these studies.

The pattern and the strength of the mutant response are taken into account in determining the mutagenicity of a chemical. All observed responses are verified in repeat tests. If no increase in mutant colonies is seen after testing several strains under several different culture conditions, the test chemical is considered to be nonmutagenic in the Salmonella test.

**Reference**

Mortelmans K, Zeiger E. The Ames Salmonella/microsome mutagenicity assay. Mutat Res. 2000 Nov 20;455(1-2):29-60.

## 5. Toxicity

Id 68551-11-1

Date 07.06.2004

### Result

:

Summary Information  
Study Vehicle: DMSO  
Protocol: Preincubation  
Result: Negative

Strain: TA100

Dose	No Act	No Act	10% RLI	10% RLI	10% HLI	10% HLI
	(Neg)	(Neg)	(Neg)	(Neg)	(Neg)	(Neg)
ug/Pt.	Mean	Mean	Mean	Mean	Mean	Mean
VC	130	0.3	133	2.9	101	10.7
3.3	123	1.9	118	9.6	116	39.1
10	137	4.6	111	7.5	119	1
33	134	4.9	115	12.5	115	5.9
100	115	4.5	137	1.8	107	7.2
220			109s	4.9		114
333	21	0			158	0
PC	1133	52	1284	34	800	36

Strain: TA1535

Dose	No Act	No Act	10% RLI	10% RLI	10% HLI	10% HLI
	(Neg)	(Neg)	(Neg)	(Neg)	(Neg)	(Neg)
ug/Pt.	Mn	sem	Mean	sem	Mean	sem
VC	27	3	33	2.3	11	0.7
3.3	27	3.8	33	1	14	1.8
10	27	3	27	2.7	15	1.8
33	27	1.2	35	0.3	15	1.2
100	22	4.3	31	2.2	12	1.8
220			25s	2.6		14
333	T	0			8	0
PC	835	13	902	21	66	3.8

Strain: TA1537

Dose	No Act	No Act	No Act	10% RLI	10% RLI	10% HLI	10% HLI
	(Neg)	(Neg)	(Neg)	(Neg)	(Neg)	(Neg)	(Neg)
ug/Pt.	Mean	sem	Mean	sem	Mean	sem	Mean
VC	6	0.7	6	0.3	5	0.7	6
3.3	8	1.2	4	0.6	6	1.5	5
10	11	1.9	5	1.2	8	1.9	7
33	11	2.3	6	0.9	5	0.6	7
100	13	2.3	5	1.5	7	2	5
220					6s	1.7	
333	173	0	339	0			12s
PC	133	10.7	468	69	370	59	73

Strain: TA98

Dose	No Act	No Act	10% RLI	10% RLI	10% HLI	10% HLI
	(Neg)	(Neg)	(Neg)	(Neg)	(Neg)	(Neg)
ug/Pt.	Mean	Mean	Mean	Mean	Mean	Mean
VC	17	1.3	18	1.5	20	1.2
3.3	18	1.3	17	2.6	20	3.2
10	12	1.2	15	2.3	23	0.7
33	16	2	22	1.2	24	4.2
100	19	1.5	19	0.6	22	2.9
220			18s	1		27
333	210	0			305	0
PC	1049	31	1289	46	544	17

Abbreviations:

PC = positive control  
VC = vehicle control  
RLI = induced male Sprague Dawley rat liver S9  
HLI = induced male Syrian hamster liver S9  
s = Slight Toxicity; p = Precipitate; x = Slight Toxicity and Precipitate; T = Toxic; c = Contamination

### Test substance

:

2-Ethylhexanol CASNO 104-76-7 (component and surrogate)

### Conclusion

:

Material was non-mutagenic in the presence or absence of standard liver metabolic activating systems

### Reliability

:

(1) valid without restriction

NTP Guideline study with data for review.

### Flag

:

Critical study for SIDS endpoint

04.01.2004

(16)

**Type** : Chromosomal aberration test  
**System of testing** : Chinese hamster ovary cells (CHO-W-B1)  
**Test concentration** : see results  
**Cytotoxic concentr.** : see results  
**Metabolic activation** : with and without  
**Result** : negative  
**Method** : other: NTP Protocol  
**Year** :  
**GLP** :  
**Test substance** : other TS

**Method** :

An in vitro assay for chromosomal damage was conducted in cloned Chinese hamster ovary cells (CHO-W-B1) to identify chemicals capable of inducing chromosomal aberrations (CA). The procedure is described in detail by Galloway et al. (1985, 1987). This assay only detects structural chromosomal damage; it does not detect aneuploidy.

Test chemicals were supplied to the testing laboratory as coded aliquots. The substance was tested in cultured CHO cells for induction of SCE and CA, both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 enzymes and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three concentrations of test substance; the high dose was limited by toxicity or solubility, or in the absence of either of these factors, the high dose was limited to 5 mg/mL. A single culture flask per concentration was used. Tests yielding equivocal or positive results generally were repeated.

Cells were harvested in their first mitotic division after the initiation of chemical exposure. Without S9, cells were incubated for 8-12 hours with the test chemical in McCoy's 5A medium supplemented with fetal calf serum, L-glutamine, and antibiotics, then Colcemid was added and incubation was continued for 2 hours. The incubation time and the dose levels selected were determined from the information on cell cycling and toxicity obtained from the prior SCE test; if cell cycle delay was anticipated, the incubation period was extended to permit accumulation of sufficient cells in first metaphase for statistical analysis. The cells were harvested by mitotic shake-off, fixed, and stained with Giemsa. For the CA test with S9, cells were treated with the test chemical and S9 for 2 hrs, after which the treatment medium was removed and the cells incubated for 10 hours in fresh medium, with Colcemid present for the final 2 hrs. Cells were harvested in the same way as for the treatment without S9.

Cells were selected for scoring on the basis of adequate morphology and completeness of karyotype (21 +/- 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. One hundred or two hundred first-division metaphase cells were scored at each dose level. The classes of aberrations that were recorded included "simple" (breaks and terminal deletions), "complex" (rearrangements and translocations), and "other" (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Data are presented as the percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted to assess the presence of a dose-response (trend test) and the significance of the individual dose points compared to the vehicle control (Galloway et al., 1987). For a single trial, a statistically significant ( $P < 0.05$ ) difference for one dose point and a significant trend ( $P < 0.015$ ) was considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A strong trend ( $P < 0.003$ ) with a single significant dose level was designated weak positive \*, to indicate a high level of induced aberrations. A

strongly positive trend ( $P < 0.003$ ), in the absence of a statistically-significant increase at any one dose point, led to an equivocal call. Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers. Trials that gave a weak positive or positive result were repeated. The overall result for the CA assay was based on an evaluation of the responses in all trials within an activation condition.

Galloway SM, Armstrong MJ, Reuben C. et al. (1987) Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluations of 108 chemicals. *Environ. Mol. Mutagen.* 10(Supplement 10): 1 - 175.

Galloway SM, Bloom AD, Resnick M et al. (1985) Development of a standard protocol for in vitro cytogenetic testing with Chinese hamster ovary cells: Comparison of results for 22 compounds in two laboratories. *Environ. Mutagen.* 7: 1-51.

## Result :

Activation	Trial	Trial Call
No Activation	1	Negative
Induced Rat Liver S9	2	Negative

Dose µg/mL	Cells	---Total Abs.---			--Complex Abs.--			--Simple Abs.--			Other Abs.	
		Abs #	Per Cell	% With Abs.	Abs #	Per Cell	% With Abs.	Abs #	Per Cell	% With Abs.	Ab #	With Abs.
Neg	0	100	0	0	0	0	0	0	0	0	0	0
DMSO	0	200	1	0.005	0.5	0	0	0	1	0.01	0.5	0
TS	50	200	3	0.015	1	1	0.01	0.5	2	0.01	1	0
TS	108	200	1	0.005	0.5	1	0.01	0.5	0	0	0	0
TS	233	200	2	0.01	1	0	0	0	2	0.01	1	0
TS	500	0	0	0	0	0	0	0	0	0	0	0
Mito	0.1	200	40	0.2	16	21	0.11	9	19	0.1	9.5	0
	0.4	50	18	0.36	26	11	0.22	18	7	0.14	14	0
Trend:			0.366			-0.001			0.2			
Probability:			0.357			0.5			0.421			

Dose µg/mL	Cells	----Total Abs.---			--Complex Abs.--			--Simple Abs.--			Other Abs.	
		Abs #	Per Cell	% With Abs.	Abs #	Per Cell	% With Abs.	Abs #	Per Cell	% With Abs.	Ab #	With Abs.
Neg	0	100	0	0	0	0	0	0	0	0	0	0
DMSO	0	200	1	0.005	0.5	0	0	0	1	0.01	0.5	0
TS	50	200	0	0	0	0	0	0	0	0	0	0
TS	108	200	0	0	0	0	0	0	0	0	0	0
TS	233	200	5	0.025	1.5	1	0.01	0.5	4	0.02	1.5	0
TS	500	0	0	0	0	0	0	0	0	0	0	0
Cyclo	5	200	32	0.16	11.5	12	0.06	5	20	0.1	7.5	0
	15	50	11	0.22	20	6	0.12	10	5	0.1	10	0
Trend:			1.346			1.343			1.346			
Probability:			0.089			0.09			0.089			

## Test substance :

2-Ethylhexanol CASNO 104-76-7 (component and surrogate)

## Conclusion :

Material did not induce chromosome aberrations in presence or absence of a metabolic activation system

## Reliability :

(1) valid without restriction

## Flag

04.01.2004

: NTP Guideline study with data for review.  
: Critical study for SIDS endpoint

(16)

## 5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

**Species** : mouse  
**Sex** : female  
**Strain** : CD-1  
**Route of admin.** : oral feed  
**Exposure period** : gd 1 to 17  
**Frequency of treatm.** : cont  
**Duration of test** :  
**Doses** : 90, 300 or 900 ppm  
**Control group** : yes, concurrent vehicle  
**Method** :  
**Year** :  
**GLP** :  
**Test substance** : other TS

**Method** : Groups of 28 pregnant Swiss (CD-1) mice were treated with 2-ethylhexanol (2EH) in feed at 0, 90, 300 or 900 ppm in feed (corresponding to 0, 0.13, 0.46, 1.49 mmol/kg-day) in a microencapsulated form to prevent reaction with feed and loss of bioavailability. Dosed feed was provided as lib from gestational day 0 to gestational day 17, at which time dams were sacrificed and the products of conception were evaluated. At sacrifice, the number of ovarian corpora lutea and uterine implantation sites, including resorptions, and dead or live fetuses, were recorded. Live and dead fetuses were weighed. Live fetuses were sexed and examined for external, visceral and skeletal malformations and variations using the standard protocols employed by the NTP for developmental toxicity evaluations in mice.

For comparative purposes, groups of pregnant mice were administered mono-2-ethylhexylphthalate (MEHP) at 0, 0.13, 0.26, 0.48, 0.97 mmol/kg-day from day 0 to gd 17 of pregnancy. Dams were sacrificed and developmental toxicity was evaluated using the same procedure as used for 2EH.

**Remark** : The maximum administered dose of 2-ethylhexanol was approximately 190 mg/kg-day. This dose produced neither maternal toxicity nor developmental toxicity. Ideally, a robust test of the developmental toxicity of 2-ethylhexanol would have included a dose level that produced maternal toxicity. In light of the finding that MEHP produced developmental toxicity at dose levels only one-sixth the maximum dose of 2-ethylhexanol that was administered, it is concluded that 2-ethylhexanol has no developmental toxicity at doses up to 190 mg/kg-day.

Support for a lack of developmental toxicity of 2-ethylhexanol comes from the di-2-ethylhexyl adipate fertility and developmental toxicity study in which a dose of 1080 mg/kg-day to Wistar rats was associated with minimal fetotoxicity and maternal toxicity. [ICI. 1988b. ICI Central Toxicology Laboratory. Di-(2-ethylhexyl)adipate (DEHA): Fertility study in rats. Report CTL/P/2229 (unpublished study). As cited in IRIS, US EPA.]

There is also a dermal developmental toxicity in which groups of 25 pregnant female Fischer 344 rats were treated cutaneously with 2-ethylhexanol at dose levels of 0, 0.3, 1.0, or 3.0 ml/kg/day for 6 hours per day on gestation days 6 through 15. No treatment-related maternal deaths or early pregnancy loss were seen in the treatment groups, but maternal

weight gain was significantly reduced during gestation day 6 through 9 in the high-dose animals. Exfoliation and crusting were seen at treatment sites at all dose levels and erythema at dose levels 1.0 and 3.0 ml/kg-day. Low-dose groups, showed an increase in postimplantation loss, decreased litter size, and reduced fetal body weights but this was not observed in the high-dose group. There were no significant increases in incidence of malformations in the 2-ethylhexanol group relative to the sham treatment group. It is concluded that 2-ethylhexanol has no developmental toxicity activity by the dermal route in rats. [Developmental toxicity evaluation of 2-ethylhexanol administered cutaneously to Fischer 344 rats (final report) with attachments and cover letters dated 032189 and 050389, Bushy Run Research Center, EPA/OTS; Doc #86-890000216]

**Result**

:

In the groups treated with 2-ethylhexanol no dams died, delivered early or were removed from study. The pregnancy rate was high (93-96%) and similar in all groups. In the control group, one litter was fully resorbed. All other pregnant animals had live litters at the gd-17 necropsy. The numbers of live litters evaluated were 27 at 90 and 300 ppm and 26 at 0 and 900 ppm levels. No maternal toxicity observed in this study as a result of 2-ethylhexanol administration. Maternal body weights, absolute weight gains, corrected weight gains, gravid uterine weight absolute liver weight and relative liver weight were similar in all groups. Food consumption was significantly increased on gestational-day 3 in the 900 ppm group but unaffected for all other time points evaluated. The calculated consumption of 2-EH, based on gestational food consumption was 0 (0 mmol/kg), 17 (0.13 mmol/kg), 59 (0.46 mmol/kg) and 191 mg/kg/day (1.49 mmol/kg), for the 0, 90, 300 and 900 ppm groups, respectively.

Exposure to dietary 2-ethylhexanol was not associated with effects on any gestational parameters. The number of corpora lutea, uterine implantation sites (live, dead, resorbed), pre- and postimplantation loss, sex ratio (% males) and live fetal body weight per litter (all fetuses or separately by sex) were similar across all groups. No treatment-related changes in the incidence of individual, external, visceral, skeletal or total malformations or variations were observed.

In contrast, MEHP increased maternal relative liver weight at doses greater than 0.48 mmol/kg and decreased corrected wt gain at 0.97 mmol/kg. Embryo/fetal mortality was increased in all MEHP-dosed groups, with the high dose producing 78% nonlive implants/litter and 63% nonlive litters. The percent litters with malformed fetuses increased at doses greater than or equal to 0.26 mmol/kg MEHP and were 12, 26, 46, 79 and 80%, control to high dose.

In conclusion, there were no maternal or developmental toxic effects of 2-ethylhexanol dietary exposure throughout gestation at any concentration tested with doses ranging as high as 191 mg/kg/day (1.49 mmol/kg). In contrast exposure to MEHP was associated with clear developmental effects at doses as low as 0.26 mmol/kg. Thus, 2-ethoxyhexanol was not associated with developmental toxicity at dose-levels approximately 6-fold greater than the dose of MEHP that produced developmental toxicity

It was concluded by the NTP "the present study indicates that 2-EH plays essentially no role in the expression of DEHP-induced maternal and developmental toxicity."

**Test substance**

:

2-Ethylhexanol CASNO 104-76-7 (component and surrogate)

## 5. Toxicity

**Id** 68551-11-1  
**Date** 07.06.2004

---

<b>Conclusion</b>	:	It was concluded by the NTP "the present study indicates that 2-EH plays essentially no role in the expression of DEHP-induced maternal and developmental toxicity."
<b>Reliability</b>	:	(1) valid without restriction
<b>Flag</b>	:	NTP Guideline study with data for review.
06.01.2004	:	Critical study for SIDS endpoint

(17) (18)

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- (1) MPBPWIN (v1.40) Program as found in EPIWIN v 3.05, Syracuse Research Corporation, Syracuse NY (April 2000).
  - (2) Sage, M; and Sage, G. Vapor Pressure. in Handbook of Property Estimation Methods for Chemicals, RS Boethling and D Mackay eds. 2000 Lewis Publishers.
  - (3) KOWWIN (v1.66) Program as found in EPIWIN v 3.05, Syracuse Research Corporation, Syracuse NY (April 2000).
  - (4) Water solubility varies for components of EP-202 from less than 1 mg/L to 6800 mg/L
  - (5) HYDROWIN program (v1.67) as found in EPIWIN v 3.05, Syracuse Research Corporation, Syracuse NY (April 2000).
  - (6) J.C. Harris in Lyman W, Reehl, W and Rosenblat, D. Handbook of Chemical Property Estimation Methods. American Chemical Society, Washington D.C. 1990, page 7-6
  - (7) EQC Level 3 Model as found in EPIWIN v 3.05, Syracuse Research Corporation, Syracuse NY (April 2000).
  - (8) Huels AG: Report No. FK 1368, 1997 (unpublished)
  - (9) Hoechst AG, unveroeffentlichte Untersuchung 79.0533, (1979) zitiert im Hoechst-GDS vom 29.04.1994 as cited in IUCLID 2000 document for 2-ethylhexanal (CASNO 123-05-7).
  - (10) BASF AG, Oekologie-Labor; unveroeffentl. Untersuchung (1165/87)
  - (11) BASF AG, Labor Oekologie; unveroeffentlichte Untersuchung, (0423/88) as cited in IUCLID 2000 document for 2-ethylhexanal (CASNO 123-05-7).
  - (12) BASF AG(1988), Labor Oekologie: Unveroeffentlichte Untersuchung: Algentest vom 16.06.1988 (2/x165/87/t72)
  - (13) BASF AG, Labor Oekologie; unveroeffentlichte Untersuchung, (0423/88) as cited in IUCLID 2000 document for 2-ethylhexanal (CASNO 123-05-7).
  - (14) BASF. Prufung der akuten oralen Toxizitat an der Ratte. Substance Oxool 740, Sub 85/420 24 Feb 1986.
  - (15) Astill BD, Deckardt K, Gembardt C, Gingell R, Guest D, Hodgson JR, Mellert W, Murphy SR, Tyler TR. Prechronic toxicity studies on 2-ethylhexanol in F334 rats and B6C3F1 mice. Fundam Appl Toxicol. 1996 29:31-9.
  - (16) Data found on NTP public database at [http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm)
  - (17) Developmental Toxicity of 2 Ethylhexanol (CAS NO. 104-76-7) in CD-1 Swiss Mice NTP Study: TER90029. Abstract available on the NTP web site and the entire report is available from NTIS.
  - (18) Price CJ; Tyl RW; Marr MC; Myers CB; Morrissey RE; Heindel JJ; Schwetz BA Developmental toxicity evaluation of DEHP metabolites in Swiss mice. Teratology 1991 May;43(5):457